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JULY 1976

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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Echocardiography in Acute Myocardial Infarction

Echocardiography in Congenital Heart Diseases

Call for Abstracts: ACC 26th Annual Scientific Session Philadelphia, February 28 to March 3, 1977

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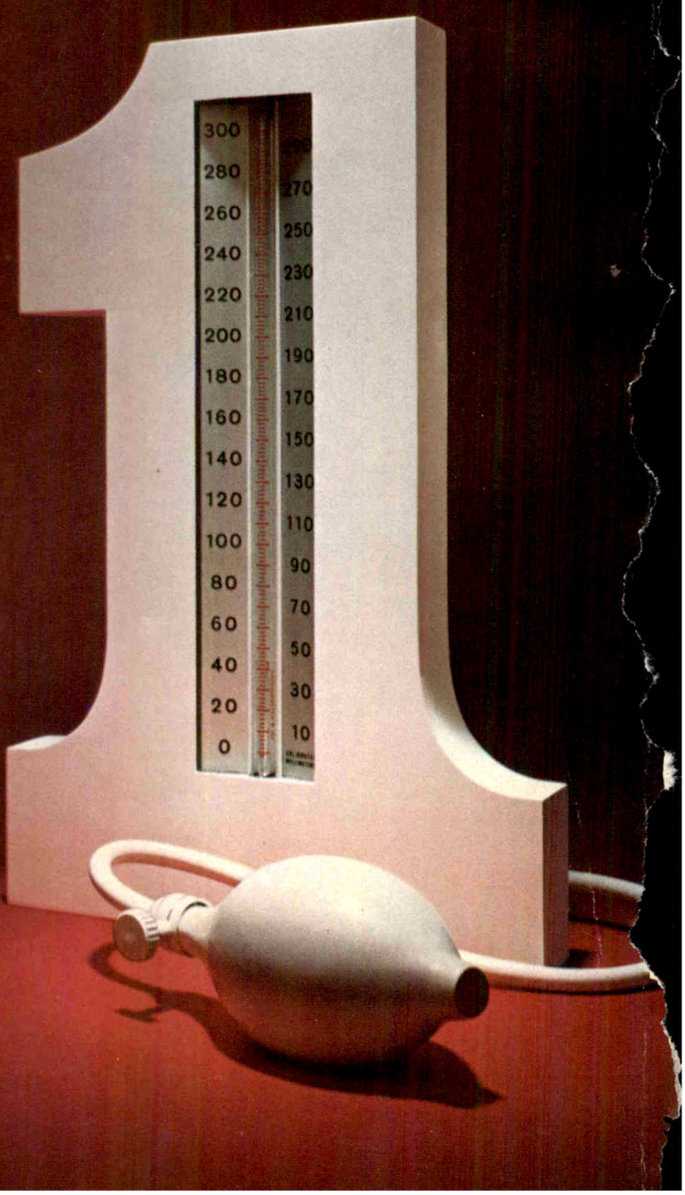
or
100 mg

can be given
once daily
in hypertension



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efficacy

Of those hypertensive patients who may be controlled by HydroDIURIL, as little as 50 mg daily may be adequate for some. In others, 100 mg a day may be required for satisfactory blood pressure control. A few patients may require 200 mg daily in divided doses.

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Single daily doses may represent a useful prescribing option, and the availability of HydroDIURIL in 50- and 100-mg tablet strengths makes the option even more useful. Once-daily therapy often represents greater convenience and fosters better compliance. (See Addendum at right for more dosage details.)

certain therapeutic limitations

Contraindications include anuria and hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs. Use with caution in patients with severe renal disease, impaired hepatic function, or progressive liver disease. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.

TABLETS: 25 mg, 50 mg, and 100 mg

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For a brief summary of prescribing information, please see following page.

addendum

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Recommended Dosage of HydroDIURIL (Hydrochlorothiazide, MSD) in Hypertension

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The usual adult starting dose is 50 mg or 100 mg as a single or divided dose. For many patients, the 50- or 100-mg tablets allow once-daily administration for convenience.

Adjusting Dosage
Dosage is increased or decreased according to the blood pressure response of the patient.

Maximum Dosage
Some patients may require up to 200 mg daily in divided doses. These patients may also benefit from the convenience of the 100-mg tablet.

Use with Other Antihypertensive Agents
HydroDIURIL often enhances the effect of other antihypertensive agents. Careful observation for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy.

P 24, 109

In hypertension

HydroDIURIL®

(Hydrochlorothiazide | MSD)

Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs; routine use in an otherwise healthy pregnant woman with or without mild edema.

Warnings: Use with caution in severe renal disease since thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.

Use in pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy or in women of childbearing potential, weigh anticipated benefit against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.
Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.
Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.
Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).
Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.
Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.
Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

How Supplied: Tablets containing 25 mg hydrochlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 50 mg hydrochlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100; Tablets containing 100 mg hydrochlorothiazide each in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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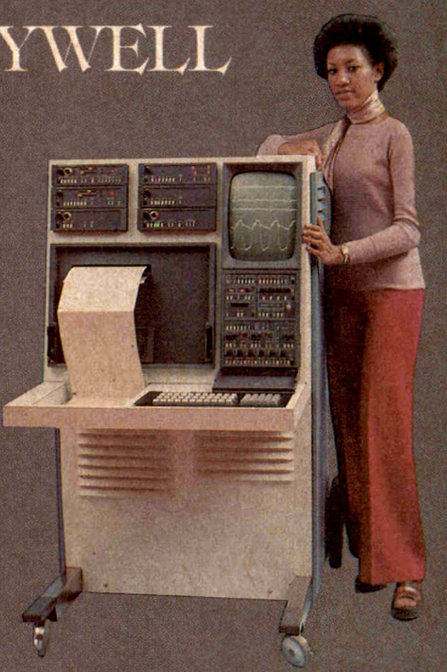

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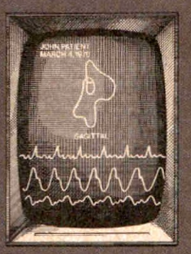

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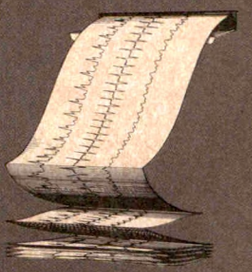

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Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

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Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.
Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

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Signs of idiosyncrasy include febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment. Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure, with digitalis intoxication, or renal insufficiency. It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

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Where such symptoms develop, or if evidence of hypotension appears, the drug should be discontinued. Gastrointestinal disturbances have only rarely been reported. If they occur, they may be minimized by administering the drug with food. If they persist, dosage should be decreased.

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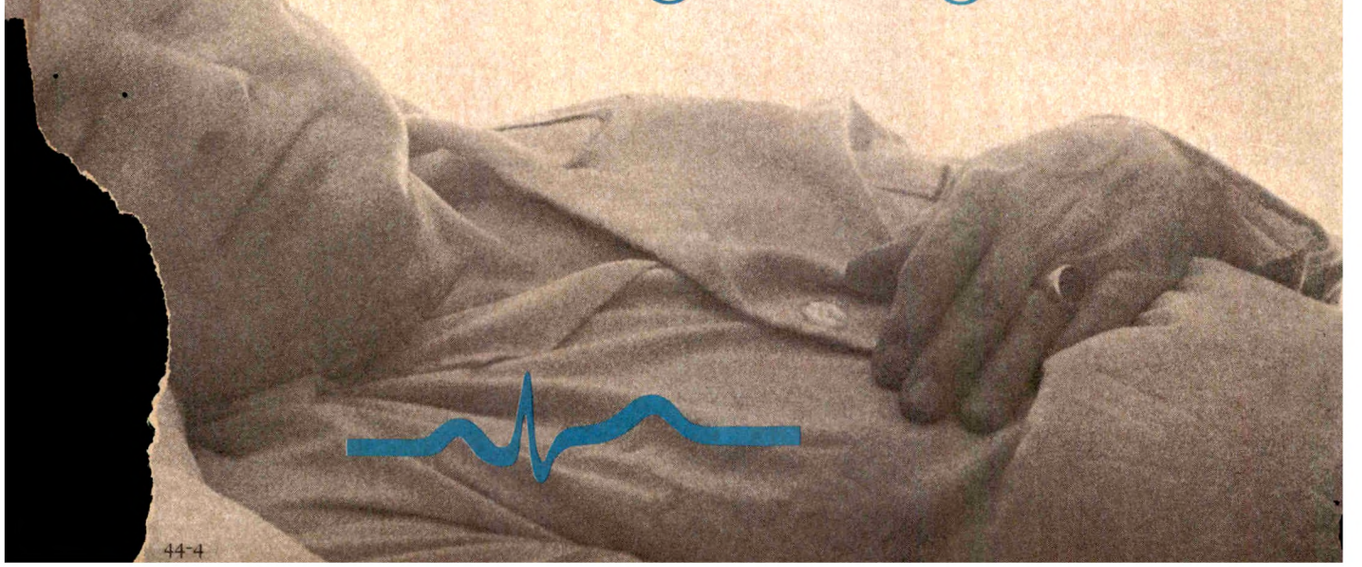

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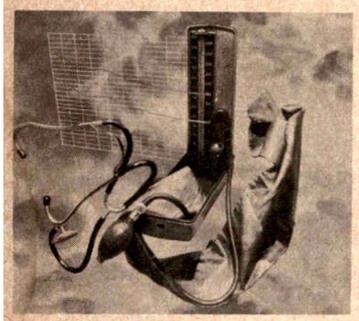

(2½) 2½ mg 5 (5) mg 10 mg (10)

Recommended Dosages Zaroxolyn® (metolazone)	
Mild to moderate essential hypertension	2½ to 5 mg once daily
Edema of cardiac failure	5 to 10 mg once daily
Edema of renal disease	5 to 20 mg once daily

NOTE: The daily dosage depends on the severity of each patient's condition, his sodium intake, and his responsiveness. Therefore, dosage adjustment is usually necessary during the course of therapy.

Prescribing Information

INDICATIONS: ZAROXOLYN (Metolazone) is indicated for the treatment of edema accompanying congestive heart failure and renal disease, and to reduce blood pressure in the management of mild to moderate essential hypertension.

CONTRAINDICATIONS: Anuria. Hepatic coma or pre-coma. Allergy or hypersensitivity to ZAROXOLYN.

The routine use of diuretics in an otherwise healthy pregnant woman, with or without mild edema, is contraindicated and possibly hazardous.

WARNINGS: While not reported to date, cross-allergy theoretically may occur when ZAROXOLYN is given to patients known to be allergic to sulfonamide-derived drugs, thiazides, or quinethazone.

Hypokalemia may occur, with consequent weakness, cramps, and cardiac dysrhythmias. It is a particular hazard in digitalized patients; dangerous or fatal arrhythmias may be precipitated.

Azotemia and hyperuricemia may be noted or precipitated during the administration of ZAROXOLYN. Infrequently, gouty attacks have been reported in persons with history of gout. Discontinue ZAROXOLYN if azotemia and oliguria worsen during treatment of patients with severe renal disease.

Presently, ZAROXOLYN is not recommended for pediatric patients.

ZAROXOLYN will, on occasion, exhibit considerable potentiation when administered concurrently with furosemide. Excessive, massive volume and electrolyte depletion may result. Exert care, especially during initial therapy, when using ZAROXOLYN with other antihypertensives. Dosage of other antihypertensive agents, especially the ganglionic blockers, should be reduced.

Use of ZAROXOLYN with a potassium-sparing diuretic may potentiate diuresis; dosage should be reduced. Potassium retention and hyperkalemia may result; serum potassium should be determined frequently. Potassium supplementation is contraindicated when a potassium-sparing diuretic is given.

USAGE IN PREGNANCY (See Contraindications): Since ZAROXOLYN crosses the placenta, and appears in the cord blood, its administration to women of child bearing-age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. The potential effects on the fetus include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

NURSING MOTHERS: ZAROXOLYN appears in breast milk. Thus it is possible that the effects of ZAROXOLYN may occur in the newborn. If the use of ZAROXOLYN is deemed essential for a nursing mother, the patient should stop nursing.

PRECAUTIONS: Periodic assessment of serum electrolytes, blood urea nitrogen, uric acid, and glucose levels should be made at intervals during therapy.

Patients receiving ZAROXOLYN therapy should be observed for clinical signs of fluid and/or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Serum potassium should be determined regularly, and potassium supplementation instituted as indicated. Hypokalemia will be more common in association with intensive or prolonged diuretic therapy, with concomitant steroid or ACTH therapy, and with inadequate electrolyte intake.

While not reported to date for ZAROXOLYN, related diuretics have increased responsiveness to tubocurarine and decreased arterial responsiveness to norepinephrine. Accordingly, it may be advisable to discontinue ZAROXOLYN three days before elective surgery.

Observe caution when administering ZAROXOLYN to hyperuricemic or gouty patients. ZAROXOLYN exerts minimal affects on glucose metabolism; insulin requirements may be affected in diabetics, and hyperglycemia and glycosuria may occur in patients with latent diabetes.

Chloride deficit and hypochloremic alkalosis may occur. In patients with severe edema accompanying cardiac failure or renal disease, a low-salt syndrome may be produced; hot weather and a low-salt diet will contribute.

Observe caution when administering ZAROXOLYN to patients with severely impaired renal function. As most of the drug is excreted by the renal route, cumulative effects may be seen in this circumstance.

Orthostatic hypotension may occur; this may be potentiated by alcohol, barbiturates, narcotics, or concurrent therapy with other antihypertensive drugs.

While not reported for ZAROXOLYN, use of other diuretics has been associated on rare occasions with pathological changes in the parathyroid glands, with hypercalcemia and hypophosphatemia.

ADVERSE REACTIONS: *Gastrointestinal reactions:* Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis. *Central nervous system reactions:* syncope, dizziness, drowsiness, vertigo, headache. *Cardiovascular reactions:* orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation and chest pain. *Hematologic:* leukopenia. *Dermatologic-hypersensitivity:* urticaria and other skin rashes. *Other reactions:* dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine; fatigue, muscle cramps or spasm, weakness, restlessness, chills and acute gouty attacks.

Adverse reactions which occur with other diuretics, but have not been reported to date for ZAROXOLYN include: pancreatitis, paresthesias, xanthopsia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity and necrotizing angiitis (cutaneous vasculitis). These reactions should be considered as possible occurrences with clinical usage of ZAROXOLYN.

Whenever adverse reactions are moderate or severe, dosage should be reduced or therapy withdrawn.

HOW SUPPLIED: Tablets, 2½, 5 and 10 mg.

References:

1. Dornfeld L, Kane R: Metolazone in essential hypertension. The long-term clinical efficacy of a new diuretic. *Curr Ther Res* **18:** 527-533, 1975.
2. Data on file, Medical Department, Pennwalt Prescription Products.

PENNWALT

Pennwalt Prescription Products
Pharmaceutical Division
Pennwalt Corporation
Rochester, New York 14603

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

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Boehringer Ingelheim Ltd., Elmsford, N.Y. 10523

Illustrated: **An English Queen**...created by L. Hewson in London in 1678.

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During more than a decade of clinical experience, compounding both science and art, Persantine has often been found useful in the long-term management of chronic angina pectoris.* It may:

eliminate or reduce the frequency of anginal attacks

improve exercise tolerance

reduce nitroglycerin requirements

Give enough...long enough (recommended dosage: 50 mg t.i.d. at least one hour before meals for 60 to 90 days or longer).

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(dipyridamole) Tablets of 25 mg

non-nitrate
coronary vasodilator

A1

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BURDICK®

JULY 1976

The American Journal of CARDIOLOGY®

VOLUME 38

NUMBER 1

CONTENTS

CLINICAL STUDIES

1 **Echoventriculography in Acute Myocardial Infarction. III. Clinical Correlations and Implication of the Noninfarcted Myocardium**

MARKKU NIEMINEN and JUHANI HEIKKILÄ

Echoventriculography detecting regional abnormalities of left ventricular wall motion demonstrates that the performance of the noninfarcted myocardium plays a significant role in the deterioration of left ventricular pump function in patients with acute myocardial infarction. The healthy myocardium is hypercontractile in uncomplicated or moderately severe infarction but is not hypercontractile or is even depressed in severe pump failure.

9 **Plasma Heparin Neutralizing Activity in Coronary Artery Disease**

BRUCE DANA, LEONARD ELLMAN, ANGELINA CARVALHO, WILLARD M. DAGGETT and ADOLPH M. HUTTER, Jr.

With the use of a new assay method increased amounts of plasma heparin neutralizing activity (which is released after platelet aggregation) were found in patients with acute myocardial infarction, unstable angina pectoris and stable arteriographically confirmed coronary artery disease. These results provide evidence for a role of platelet aggregation in coronary artery disease.

12 **Spectrum of Coronary Artery Disease in Idiopathic Hypertrophic Subaortic Stenosis**

ABE WALSTON, II and VICTOR S. BEHAR

Six of 42 patients (15 percent) with idiopathic hypertrophic subaortic stenosis showed significant atheromatous coronary artery disease, and another 3 had coronary arterial anomalies. The incidence of atheromatous coronary disease increased with age. There was no correlation with severity of chest pain or presence of electrocardiographic signs of myocardial infarction.

EXPERIMENTAL STUDIES

17 **Effects of Excess Glucose and Insulin on Glycolytic Metabolism During Experimental Myocardial Ischemia**

A. JAMES LIEDTKE, HOWARD C. HUGHES and JAMES R. NEELY

These data show no obvious benefits of glucose and insulin supplements, infused directly into the ischemic myocardium, on either mechanical or metabolic functions during experimental myocardial ischemia in an intact working swine heart preparation. An alternative explanation for the reported experimental and clinical efficacy of glucose-insulin-potassium infusions must be sought.

Continued on page A17

Why his physician chose a CPI Pacemaker

Because, of the three major pacemaker companies, CPI is No. 1 in *lithium*. A proven pacemaker power source that has experienced no battery failures in over 3 years of clinical use in over 10,000 implants. Specialized hybrid circuitry and exacting quality assurance contribute to a drastically-reduced failure rate. Body fluid contamination of the pulse generator interior is eliminated, due to a triple hermetic seal.

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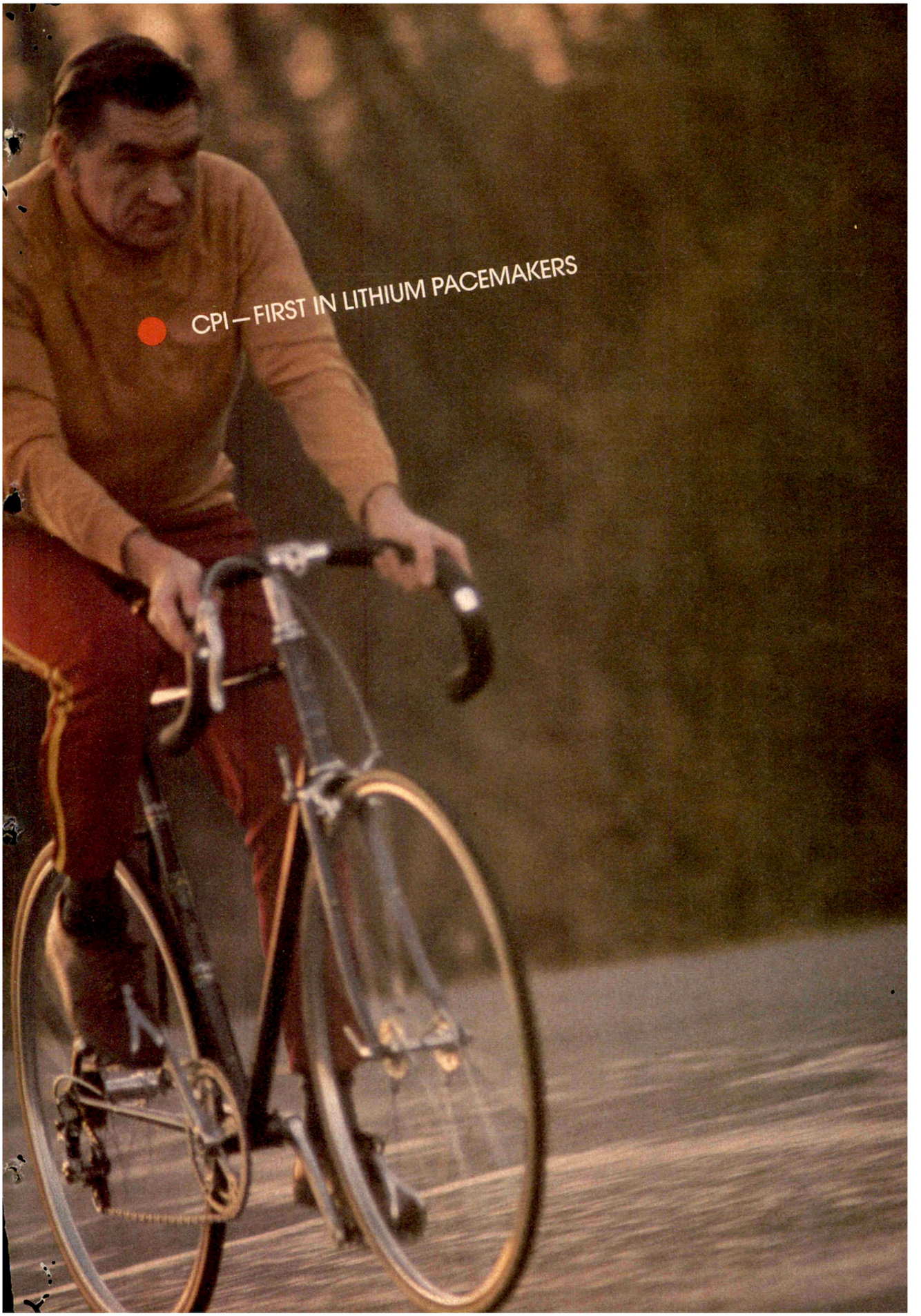
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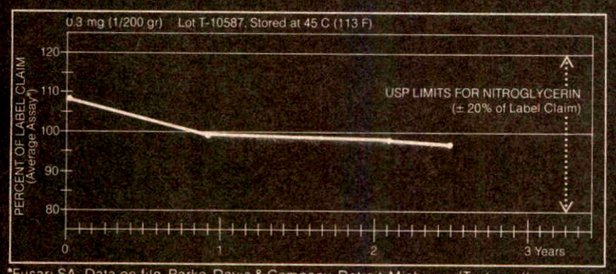
Heat-stable? Yes. Up to 45 C (113 F), considerably higher than "vest pocket" temperatures.



*Fusari SA. Data on file, Parke, Davis & Company, Detroit, Michigan. (Test results were similar for the 0.4-mg and the 0.6-mg strengths.)

Potency and Content Uniformity? The average assay still shows almost 100% of label claim more than 30 months after manufacture. What's more, the crucial question of maintenance of content uniformity of nitroglycerin is answered by Nitrostat as proved by assay: less chance of your patient taking a superpotent or, more important, a subpotent tablet.

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PARKE-DAVIS *PARKE, DAVIS & COMPANY, Detroit, Michigan 48232*

CONTENTS

28 **Failure of Hyaluronidase to Alter the Early Course of Acute Myocardial Infarction in Pigs**

ALBERT S. MOST, ROBERT J. CAPONE and PATRICIA A. MASTROFRANCESCO

Contrary to its reported benefits in dogs, hyaluronidase did not alter the early course of acute myocardial infarction in closed chest anesthetized pigs, as studied by precordial S-T segment mapping and changes in ventricular wall motion. Species difference may be responsible since the infarct in pigs may be less amenable to modification by pharmacologic intervention.

METHODS

34 **Simple Method for Computer-Aided Analysis of Echocardiograms**

SHELLEY I. SAFFER, J. V. NIXON and DAVID J. MISHELEVICH

This simple method utilizing a sonic digitizing tablet permits usually laboriously obtained information to be obtained by computer-aided analysis of M-mode echocardiograms. A program has been written to compute and type the results of standard calculations involving mitral valve motion and left ventricular function.

38 **Monitoring Tissue Oxygenation of the Heart After Myocardial Revascularization**

LESLIE WIENER, MARIO FEOLA, JOHN Y. TEMPLETON, III, *with the technical assistance of* HENRY M. HAMARMAN and ALAGAR R. VENKATASWAMY

Simultaneous monitoring of myocardial tissue oxygen tension (MPO_2) and intramyocardial electrograms by polarography in dogs revealed reduced MPO_2 and elevated S-T segments when the blood flow to the sample area was reduced 50 percent or more. This technique also proved sensitive, useful and reliable in nine patients undergoing aortocoronary bypass surgery. MPO_2 increased in the revascularized areas and decreased significantly when the graft was occluded.

EPIDEMIOLOGY

46 **A General Cardiovascular Risk Profile: The Framingham Study**

WILLIAM B. KANNEL, DANIEL McGEE and TAVIA GORDON

This paper presents an economic and efficient method for identifying persons at high cardiovascular risk who require preventive care and those at low risk who do not. The method utilizes a composite "risk function" score based on serum cholesterol, systolic blood pressure, glucose tolerance, electrocardiographic evidence of left ventricular hypertrophy and cigarette smoking. The 10 percent of persons who were identified with use of this risk function as being at highest risk accounted for one fifth of the 8 year incidence of coronary heart disease and about one third of the incidence of atherothrombotic brain infarction, hypertensive heart disease and claudication.

Continued on page A19

IN CARDIAC OR CEREBROVASCULAR DISEASE

where straining at stool may be hazardous

Effectively help avoid straining

Clinicians have recommended that SENOKOT laxatives be used routinely to *avoid* constipation in cardiac patients, as a possible means of reducing deaths and accidents due to straining at stool.[1] Routine use of SENOKOT laxatives for cerebrovascular patients has also helped prevent effects of excessive straining which may lead to transient cerebral ischemia in the elderly.[2]

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SENOKOT Tablets/Granules permit dosage adjustment for regular and comfortable evacuation, according to patient requirements. A gentle, predictable overnight laxative, SENOKOT preparations are usually free of side effects at proper dosage levels. With their virtually colon-specific action,[3] SENOKOT Tablets/Granules are compatible with other medication patients may be taking.

References: 1. McGuire, J., *et al,* cited in Exton-Smith, A. Norman: Constipation in Geriatrics, in *Management of Constipation,* edited by Sir Francis Avery Jones and Edmund W. Godding, Oxford, Blackwell Scientific Publications, 1972, p. 162. **2.** Halpern, A., *et al,* cited in Exton-Smith, A. Norman, *ibid.* **3.** Godding, E. W.: Therapeutic Agents, in *Management of Constipation, op cit* (ref. 1), p. 65.

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SENOKOT® tablets granules

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a natural vegetable laxative

Senokot laxative claims are documented

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PEDIATRIC CARDIOLOGY

53 Discrete Subvalvular Aortic Stenosis in Childhood. Study of 51 Patients

EDGAR A. NEWFELD, ALEXANDER J. MUSTER, MILTON H. PAUL, FAROUK S. IDRISS and WILLIAM L. RIKER

In this series of 51 children with discrete subvalvular aortic stenosis, there were three anatomic types of obstruction, namely, thin membranous type (43 cases), fibromuscular collar type (5 cases) and funnel type (3 cases). Associated cardiac defects in 57 percent of the children often masked the typical clinical and cardiac catheterization features of subaortic stenosis. Criteria for operability include the angiographic demonstration of a discrete subvalvular diaphragm and a resting left ventricular to aortic systolic pressure gradient of 40 mm Hg or greater.

62 Pulmonary Blood Flow Distribution in Transposition of the Great Arteries

BERNARDO A. VIDNE, DIANA DUSZYNSKI and S. SUBRAMANIAN

Before undergoing the Mustard intraatrial baffle operation for transposition of the great arteries, 21 patients had normal distribution of pulmonary blood flow (determined by scintillation scanning of the lungs), 10 had preferential flow to the right lung and 3 had preferential flow to the left lung. After operation, 19 had a normal pattern, 21 had preferential flow to the right lung and 3 had preferential flow to the left lung. The postoperative scanning studies have helped to exclude recurrence of the shunt, pulmonary or systemic venous obstruction and development of pulmonary hypertension.

67 Echocardiographic Localization of Interatrial Baffle After Mustard Operation for Dextrotransposition of the Great Arteries

KALIM U. AZIZ, MILTON H. PAUL and ALEXANDER J. MUSTER

Echocardiography consistently located the interatrial baffle behind the pulmonary arterial root and measured a dimension of the new systemic venous atrium and the posterior segment of the pulmonary venous atrium with reliable accuracy using the mitral-pulmonary valve continuity as a reference point. Such measurements may help evaluate the growth in size of these structures.

73 Echocardiographic Detection of Large Left to Right Shunts and Cardiomyopathies in Infants and Children

DAVID J. SAHN, YVONNE VAUCHER, DAVID E. WILLIAMS, HUGH D. ALLEN, STANLEY J. GOLDBERG and WILLIAM F. FRIEDMAN

Echocardiographic measurements in normal premature and full-term infants revealed that the mean velocity of circumferential fiber shortening was significantly lower than in infants with a large shunt and higher than in infants with nonstructural heart disease. The ratio of left atrial to aortic root diameter at end-systole was comparable in the group with a large shunt and nonstructural heart disease and significantly higher in both groups than in normal patients. Similar echocardiographic features distinguished older children with cardiomyopathy from normal children.

Continued on page A21

IN ANGINA*: **ACTS WITH SUBLINGUAL SPEED**

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ISOSORBIDE DINITRATE

As with sublingual ISDN:
acts in 2 minutes for therapeutic use...
acts up to 2 hours for prophylaxis.

In addition:
chewing action helps distribute nitrate over a larger mucosal area.

SUMMARY OF
PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

* **Indications:** Based on a review of this drug by The National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: Sublingual and chewable dosage forms of SORBITRATE are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.
Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.
Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.
Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.
This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.
Dosage and Administration: Route: Sublingual, oral and chewable tablets.
Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.
Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:
Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.
Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.
It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS
Division of ICI United States Inc.
Wilmington, Delaware 19897

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CONTENTS

80 **Echocardiographic Manifestations of Single Ventricle**

JOEL M. FELNER, DOROTHY B. BREWER and ROBERT H. FRANCH

The absence of a ventricular septum in a patient with two atrioventricular (A-V) valves on echocardiography enhances the diagnosis of a single ventricle. This echocardiographic study of eight patients with a single ventricle revealed an absent ventricular septum in six, a bulboventricular ridge in two and two A-V valves in all subjects.

REVIEWS

85 **Double Outlet Right Ventricle: Hemodynamic and Anatomic Correlations**

SOMKID SRIDAROMONT, ROBERT H. FELDT, DONALD G. RITTER, GEORGE D. DAVIS and JESSE E. EDWARDS

In this Mayo Clinic review of 62 patients with double outlet right ventricle, the most frequent anatomic combination was the side to side relation of the great arteries with subaortic ventricular septal defect (28 patients). Pulmonary stenosis was present in half the cases. In all 13 patients with subpulmonary ventricular septal defect, pulmonary arterial oxygen saturation was greater than systemic, regardless of the relation of the great arteries. In the patients with subaortic ventricular septal defect, pulmonary arterial oxygen saturation greater than systemic arterial saturation was not reliable evidence of a Taussig-Bing anomaly. The latter was present in only 4 of 25 patients with such saturation.

REPORTS ON THERAPY

95 **Metabolic Consequences of Glucose-Insulin-Potassium Infusion in Treatment of Acute Myocardial Infarction**

JOHN W. PRATHER, RICHARD O. RUSSELL, Jr., JOHN A. MANTLE, HUEY G. McDANIEL and CHARLES E. RACKLEY

This study in 18 patients with acute myocardial infarction demonstrates that, although glucose-insulin-potassium infusion is relatively safe, serum electrolytes and glucose levels should be serially monitored. Hyperkalemia during infusion was the most serious potential complication and should be treated by reducing the concentration of potassium ion in the infusate; hyperkalemia after discontinuation of the infusion is treated with sodium polystyrene sulfonate orally or by rectal enema. The clinical benefit of such treatment is not discussed.

100 **Diabetic Treatment and Primary Ventricular Fibrillation in Acute Myocardial Infarction**

EDGAR LICHSTEIN, LESLIE A. KUHN, EMANUEL GOLDBERG, MICHAEL N. MULVIHILL, HARRY SMITH, Jr. and THOMAS C. CHALMERS

Primary ventricular fibrillation developed in 5.3 percent of 265 patients with diabetes mellitus and acute myocardial infarction. No statistically significant association was found between the incidence of ventricular fibrillation and the type of treatment (diet, insulin or oral hypoglycemic agents) for diabetes mellitus.

Continued on page A23

NEW from Sonicaid:

The ruggedly constructed, AC powered Sonicaid BV380 can be easily transported from room to room as needed. The pencil-like transducer transmits and then receives the reflected ultra-sound signal (doppler shift) which is then processed by Sonicaid's advanced circuitry for both audio and visual presentation.

As an alternative, Sonicaid offers the BV381, the same as the BV380, but with an integral 2-speed, 2-channel chart recorder with ECG/PCG facility.

the BV380 Blood Velocimeter

Non-invasive, doppler ultra-sound, blood velocity measurement for cardiologists, vascular and cardiovascular surgeons, internists and neurologists, general practitioners.

The new, simple to operate, Sonicaid BV380 Blood Velocimeter obtains data on both blood velocity and direction by doppler ultra-sound. A non-invasive, transcutaneous procedure, it offers no discomfort to the patient.

A narrow beam of low energy (4 or 8 MHz) ultrasound is transmitted into a blood vessel. The signal reflected from the blood cells is then processed by Sonicaid's advanced circuitry to yield both blood flow and direction data.

Both Audio and Visual Presentation

The meter on the BV380's front indicates both blood velocity and direction and there are separate outputs to link the BV380 to a standard ECG recorder or oscilloscope.

You can listen to the representation of blood flow sounds on either a loudspeaker or headset with a stereo effect. And you can connect a stereo tape recorder to transcribe the signal.

Interpretation and Application

To assist you in the recognition of blood velocity waveforms symptomatic of a variety of circulatory ailments, we have prepared an atlas: "Blood Velocity Waveforms and their Physiological Interpretation." Applications where the BV380 can assist you include:

- diagnosis of diseases of the right and left heart
- examination of the peripheral arterial system
- determination of patency following reconstructive surgery
- determination of venous incompetence
- neurological investigations related to diseases of the carotid and ophthalmic arteries

The BV380 has proved to be a practical alternative to catheterization or angiograms in a number of cases where the patient was too ill to undergo these procedures.

For more information

For further information or a demonstration of the new Sonicaid BV380 Blood Velocimeter or its companion BV381 with an integral 2-speed, 2-channel recorder with ECG/PCG facility, please write John Scales, Executive Vice-President, Sonicaid, Inc.

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a pioneer and world leader in doppler ultra-sound diagnostics...more than 20,000 of our most popular instrument, a fetal heart detector, are in use in more than 91 countries...the BV380 and BV381 are sold and serviced nationwide.

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CONTENTS

103 Influence of Dobutamine on Hemodynamics and Coronary Blood Flow in Patients With and Without Coronary Artery Disease

STEVEN L. MEYER, GEORGE C. CURRY, MICHAEL S. DONSKY, DONALD B. TWIEG, ROBERT W. PARKEY and JAMES T. WILLERSON

Dobutamine may have some advantages over certain other inotropic agents in that it increased myocardial contractility and cardiac output with relatively small effect on heart rate in 18 patients undergoing cardiac catheterization and coronary arteriography. However, in patients with severe coronary artery disease it increased coronary arterial perfusion less than in patients without such disease and the pattern of perfusion became more inhomogeneous.

CASE REPORTS

109 Mitral Valve Malformation of Ebstein Type in Absence of Corrected Transposition

DAVID G. RUSCHHAUPT, SAROJA BHARATI and MAURICE LEV

In this first documented case of mitral valve malformation of the Ebstein type in the absence of corrected transposition, the ring of the inferior leaflet of the mitral valve was displaced downward, dividing the left ventricle into a proximal atrialized and a distal effective ventricular chamber. The infant died less than 48 hours after birth.

113 Surgical Correction of Truncus Arteriosus in Infancy

HENRY SULLIVAN, RABI SULAYMAN, ROBERT REPLOGLE and RENE A. ARCILLA

A modification of the Rastelli procedure using a prosthetic conduit with an attached porcine valve was successfully employed to correct a type I truncus arteriosus in an 8 week old infant with severe heart failure. Such palliative surgery converts cardiac function to a more normal state and simplifies future surgical interventions.

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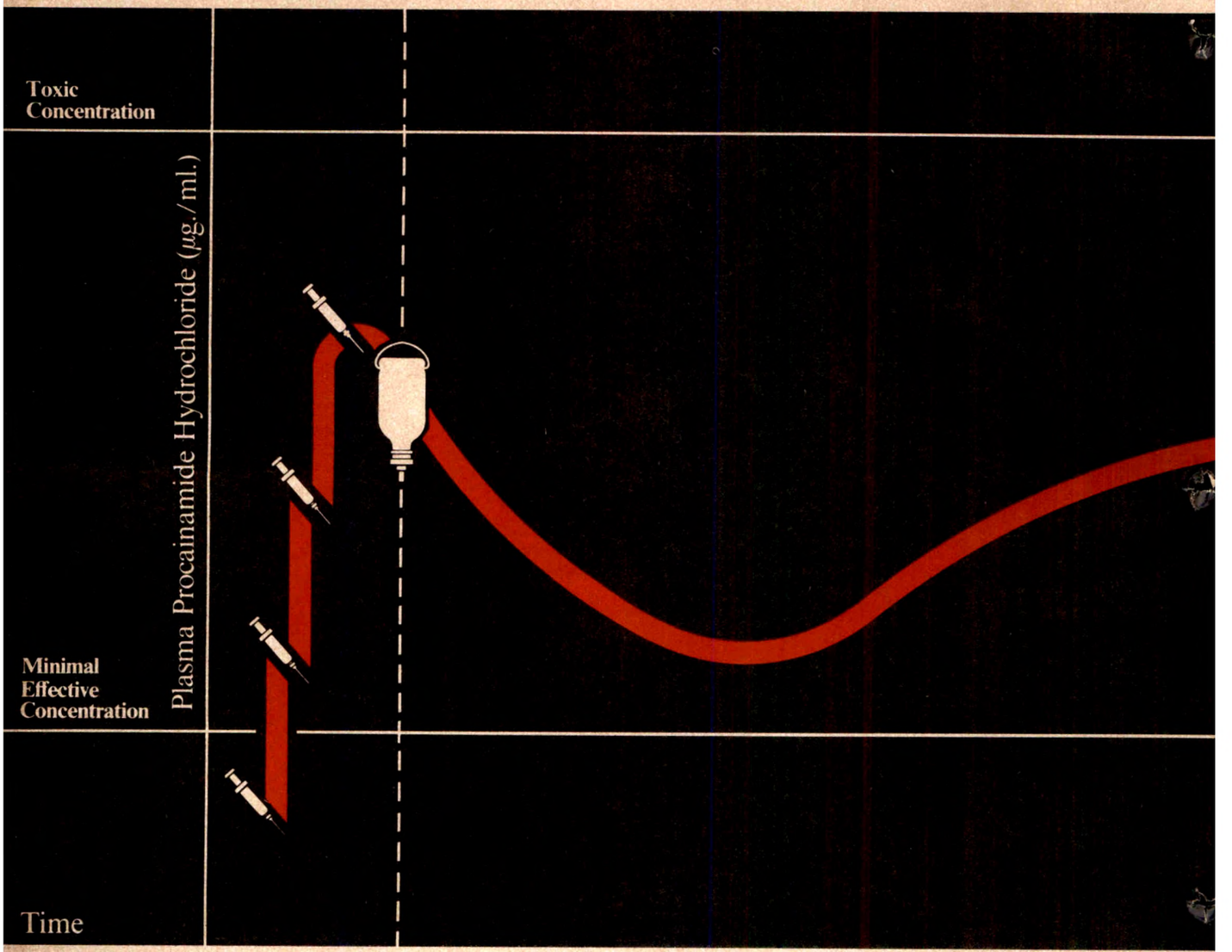

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100 mg. every 5 minutes
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to be administered at a rate
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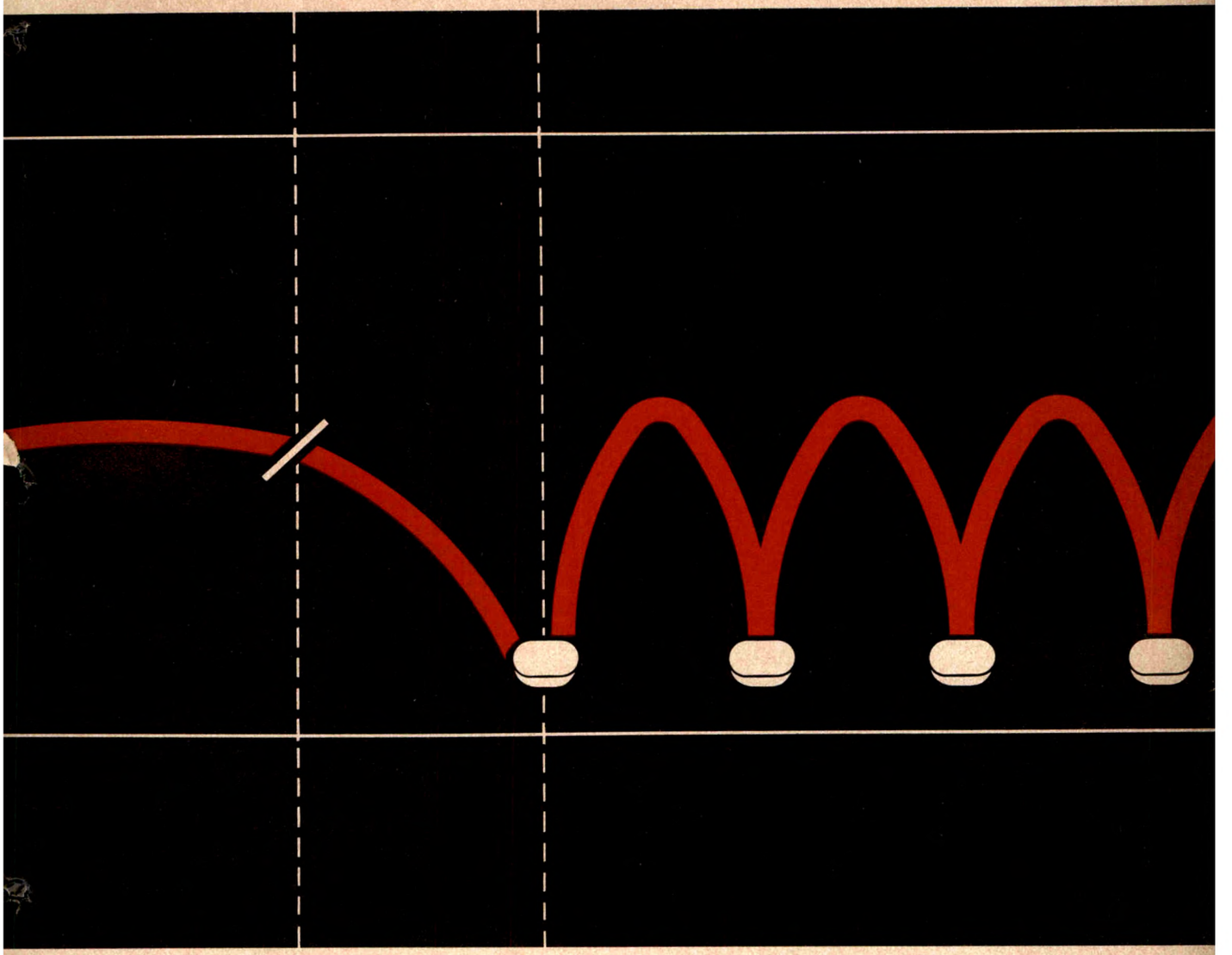

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4 hours
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through the entire therapeutic course

See next page for brief summaries.

For Ventricular Arrhythmias

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Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. *Intravenous use should be limited to extreme emergencies,* **the drug should be administered as a dilute infusion,** and the patient should be monitored electrocardiographically. The intravenous dose should not exceed 1 gram. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions.

How Supplied: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is available in 10 ml. vials providing 100 mg./ml. and in 2 ml. vials providing 500 mg./ml.

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(Procainamide Hydrochloride Tablets)

> The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

Pronestyl Tablets (Procainamide Hydrochloride Tablets) are veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

Administration: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

How Supplied: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100. The 250 mg. and 500 mg. tablets are also available in bottles of 1000.

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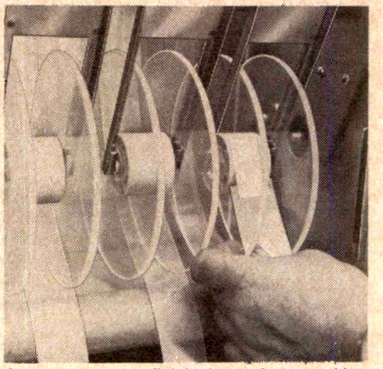

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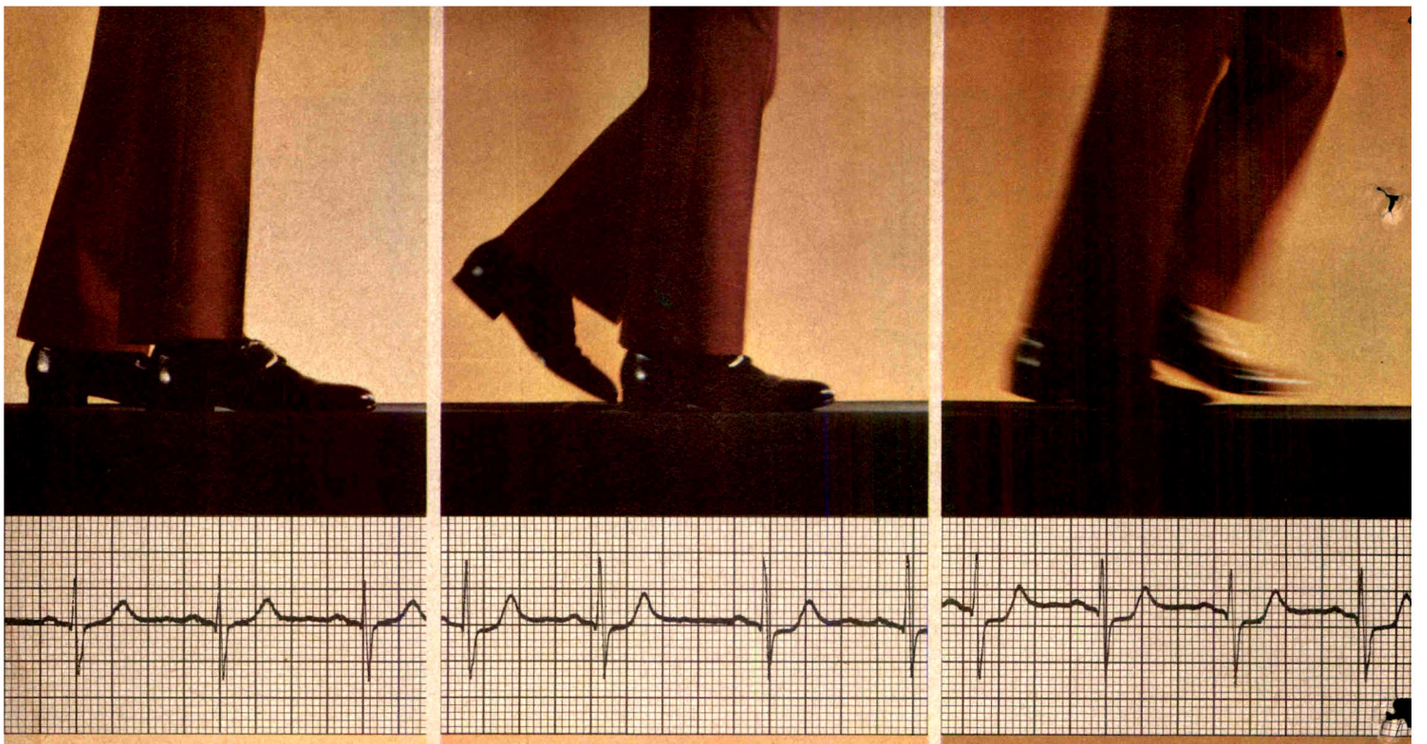

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4th Minute at 2 mph, 0% Grade, V-5, HR-75. Base line stability is maintained because of the electrode's gel retaining cup and gel impregnated foam pad; the gel pad is slightly oversize to assure positive, continuous pressure at the electrode-skin interface. The result: virtual elimination of base line instability and motion artifact.

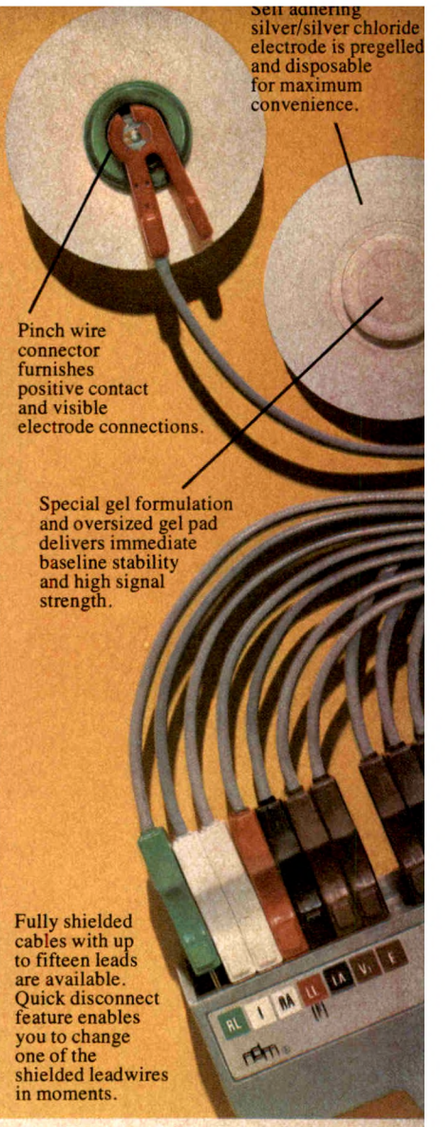
4th Minute at 3 mph (8th minute of test), 0% Grade, V-5, HR-83. (The patient's ECG indicates 1 mm of S-T depression.) Fully shielded cable and leadwire provide an effective barrier to the electrical interference that might otherwise mask small amounts of S-T depression.

Do your stress test ECGs show everything you need to see?

4th Minute at 3 mph (12th minute of test), 5% Grade, V-5, HR-117. (S-T depression increases to 2.5 mm.) Even at high work loads, the American Stress Test Electrode and fully shielded cable system delivers a stable base line and noise-free signal.

4th Minute at 3 mph (16th minute of test), 7.5% Grade, V-5, HR-135. (S-T depression drops to 2.0 mm.) Long test procedures seldom affect the electrode's contact with a patient's skin; trace quality remains high, even with patients who perspire heavily.

(Because of this electrode's special gel formulation, application periods of longer than four hours are not recommended.)



Compare the stress test electrocardiograms you have been getting with those reproduced above.* There's a reason for the unusually high quality of the ECG traces shown: The patient was being monitored with American's Stress Test Electrode and fully shielded cable system.

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*Examples shown were produced under clinical conditions during an actual stress test procedure using the American Stress Test Electrode system.

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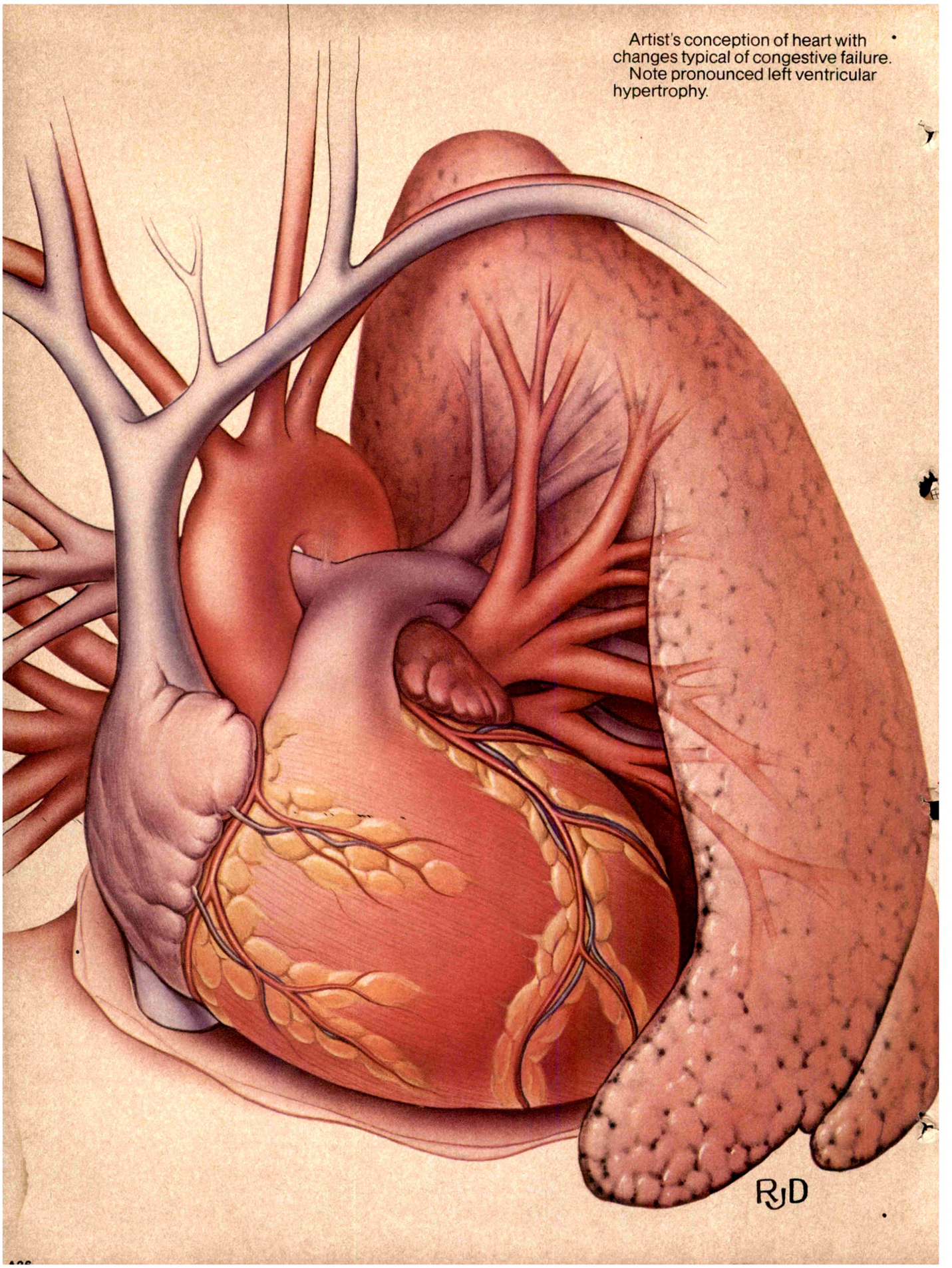

Artist's conception of heart with changes typical of congestive failure. Note pronounced left ventricular hypertrophy.

In congestive heart failure...

aldosteronism promotes edema. "The hyperaldosteronism present in the majority of patients with congestive heart failure...explains the low sodium excretion in urine, sweat, and saliva. Ultimately, of course, this retention of salt and water leads to edema."[1]

Aldactone (spironolactone) combats aldosteronism... promotes diuresis.

"By administering spironolactone [Aldactone] over, say, three or four weeks, one may actually induce a greater sodium and water loss than with more powerful natriuretic agents. . . ."[2]

Effective diuresis in edema of congestive heart failure

Aldactone® (spironolactone) 25-mg. tablets

- Produces gradual, positive, sustained diuresis, usually without causing acute volume depletion, and without rebound fluid retention.
- Helps prevent potassium loss which may contribute to arrhythmias and digitalis toxicity.

See next page for brief summary of prescribing information.

In congestive heart failure

Aldactone®

(spironolactone)

25-mg. tablets

Indications—Essential hypertension; edema of congestive heart failure, cirrhosis of the liver, the nephrotic syndrome and idiopathic edema. Some patients with malignant effusions may benefit from Aldactone (spironolactone), particularly when given with a thiazide diuretic.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of renal function, anuria and hyperkalemia.

Warnings—Potassium supplementation may cause hyperkalemia and is not indicated unless a glucocorticoid is also given. Discontinue potassium supplementation if hyperkalemia develops. **Usage of any drug in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the mother and fetus.**

In a 78-week chronic toxicity study, rats were given daily oral doses of spironolactone approximately 30, 90 and 300 times the usual daily human therapeutic dose (100 mg. per day). The results of this study demonstrated a dose-related, statistically significant increase in the occurrence of benign adenomas of the testes and thyroid gland. Similar findings have not been demonstrated in other animal studies. In view of the marked differences in spironolactone metabolism by the rat and by man, the relationship of this finding to the possible development of tumors in humans is unknown.

Precautions—Patients should be checked carefully since electrolyte imbalance may occur. Although usually insignificant, hyperkalemia may be serious when renal impairment exists; deaths have occurred. Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, together with a low serum sodium may be caused or aggravated, especially when Aldactone is combined with other diuretics. Elevation of BUN may occur, especially with preexisting renal impairment. Mild acidosis may occur. Reduce the dosage of other antihypertensive drugs, particularly the ganglionic blocking agents, by at least 50 percent when adding Aldactone since it potentiates their action. The physician should be alert to the possible onset of gynecomastia.

Adverse Reactions—Drowsiness, lethargy, headache, diarrhea and other gastrointestinal symptoms, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, gynecomastia, inability to achieve or maintain erection, androgenic effects, including hirsutism, irregular menses and deepening voice. Adverse reactions are usually reversible. In rare instances gynecomastia may persist.

Dosage and Administration—**For essential hypertension in adults** the initial daily dosage is 50 to 100 mg. in divided doses. Aldactone may be combined with a thiazide diuretic if necessary. Continue treatment for two weeks or longer since the maximal response may not occur sooner. Adjust subsequent dosage according to response of patient.

For edema in adults initial daily dosage is 100 mg. in divided doses. Continue medication for at least five days to determine diuretic response; add a thiazide or organic mercurial if adequate diuretic response has not occurred. Aldactone dosage should not be changed when other therapy is added. A daily dosage of Aldactone considerably greater than 75 mg. may be given if necessary.

A glucocorticoid, such as 15 to 20 mg. of prednisone daily, may be desirable for patients with extremely resistant edema which does not respond adequately to Aldactone and a conventional diuretic. Observe the usual precautions applicable to glucocorticoid therapy; supplemental potassium will often be necessary. Such patients frequently have an associated hyponatremia—restriction of fluid intake to 1 liter per day or administration of mannitol or urea may be required (these measures are contraindicated in patients with uremia or severely impaired renal function). Mannitol is contraindicated in patients with congestive heart failure, and urea is contraindicated with a history or signs of hepatic coma unless the patient is receiving antibiotics orally to "sterilize" the gastrointestinal tract.

Glucocorticoids should usually be given first to patients with nephrosis since Aldactone, although useful for diuresis, will not directly affect the basic pathologic process.

For children the daily dosage should provide 1.5 mg. of Aldactone per pound of body weight.

References:

1. Genest, J., and Nowar, T.: Clinician: Congestive Heart Failure, Medcom* Learning Systems, New York, Medical Communications, Inc., 1972, pp. 42-49.
2. Laragh, J. H.: Hosp. Pract. 5:43-50 (Nov.) 1970.

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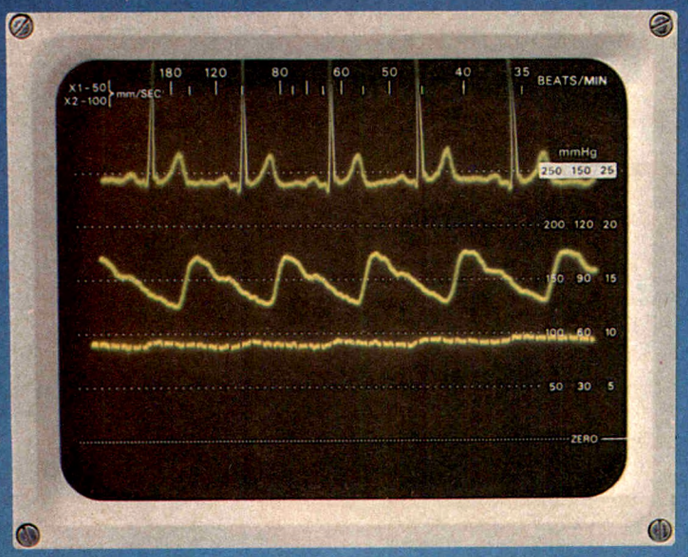

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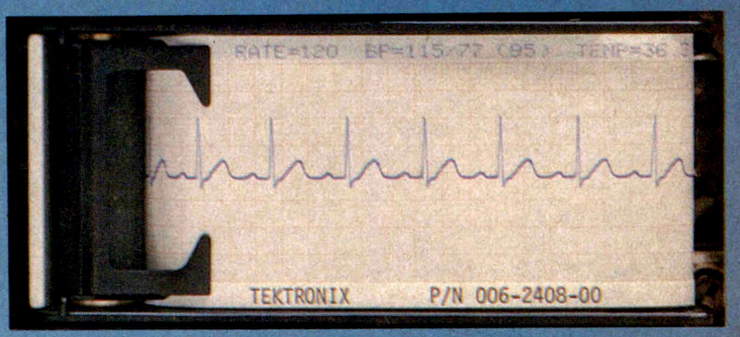

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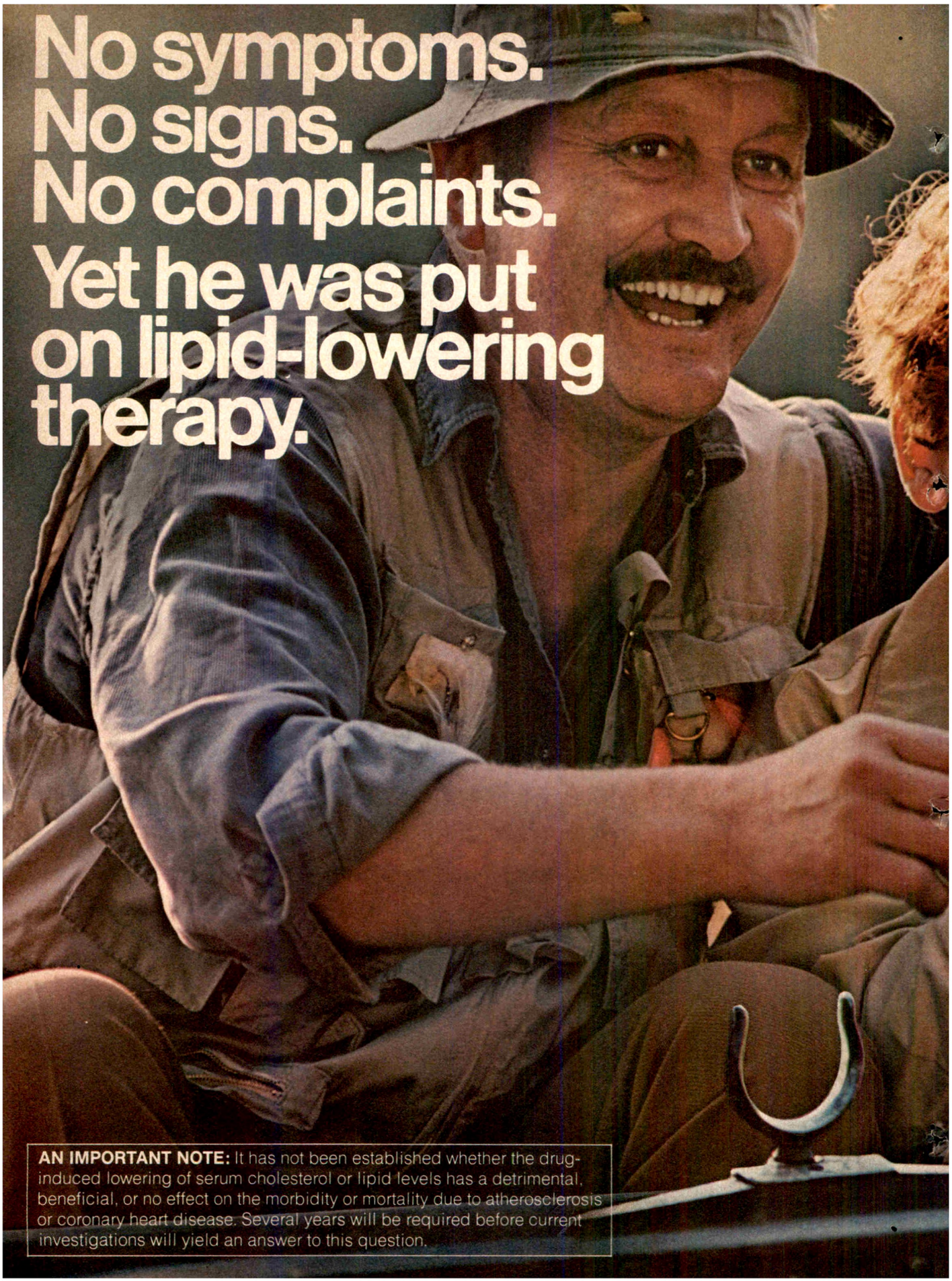
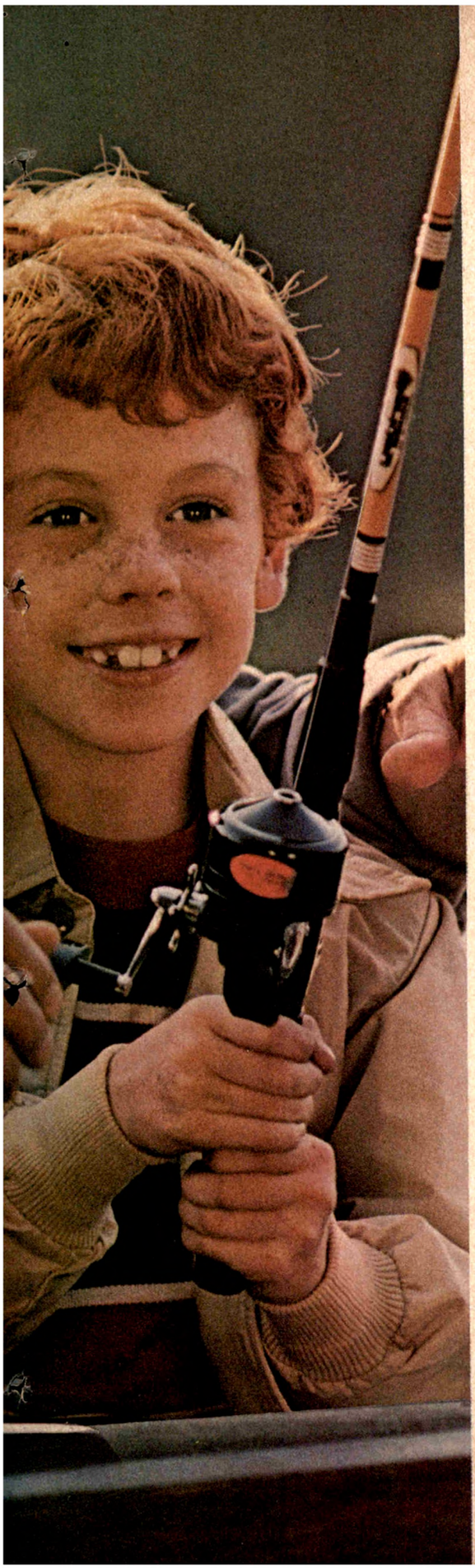

No symptoms.
No signs.
No complaints.
Yet he was put
on lipid-lowering
therapy.
AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.



Early intervention — a rational approach to the management of hyperlipidemia

Reducing elevated lipid levels is a rational therapeutic goal at any stage of the hyperlipidemic process. Lipid lowering is perhaps most logical, however, early in the course of hyperlipidemia, when most patients are asymptomatic.[1]

Seemingly well, these patients are usually found to be hyperlipidemic when routine cholesterol *and* triglyceride determinations are performed as part of an overall clinical and laboratory workup.

If persistent, clinically significant lipid elevations are demonstrated—and underlying disease states are ruled out through history, physical examination, and appropriate laboratory tests—a diagnosis of primary hyperlipidemia is confirmed.

Dietary modification directed at correcting the specific lipid abnormality should be instituted as the first therapeutic step, but often fails to lower the lipids sufficiently.

This is the best time to add ATROMID-S, an antilipidemic agent, to the regimen. Early, effective, and continuous lipid lowering is important in the successful management of hyperlipidemia.

Routine testing for both cholesterol *and* triglycerides recommended

The concept of early intervention is gaining acceptance in dealing with the nationwide epidemic of hyperlipidemia. As a result, there is a trend toward increased screening of both asymptomatic patients and blood relatives of hyperlipidemic patients. "Because history and physical examination are limited in their ability to detect these disorders [hypercholesterolemia and hypertriglyceridemia], it now appears mandatory that each physician screen each patient routinely for lipid abnormalities just as one now routinely gets a hematocrit, a urinalysis or a fasting blood sugar in the course of an annual physical examination."[1]

Hyperlipidemia

Atromid-S®

Ayerst®

(clofibrate) Capsules 500 mg.

See next page of advertisement for prescribing information.

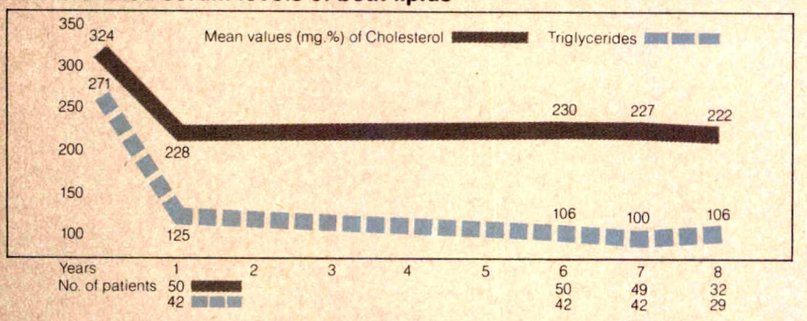
Hyperlipidemia—a factor you can do something about

You cannot change your patient's heredity. Or sex. Or age. But you can help alter other factors in his profile: improper diet, excessive smoking, hypertension *and* hyperlipidemia. While diet is the starting point in the management of primary hyperlipidemia, it is not always successful. As Zelis[2] points out: "Dietary control requires strong motivation and self-discipline that not every patient is able to exercise." And even under carefully monitored dietary regimens, lipid lowering may be inadequate. For these reasons, it is often necessary to add an antilipidemic agent such as ATROMID-S to produce significant reductions in serum lipids.

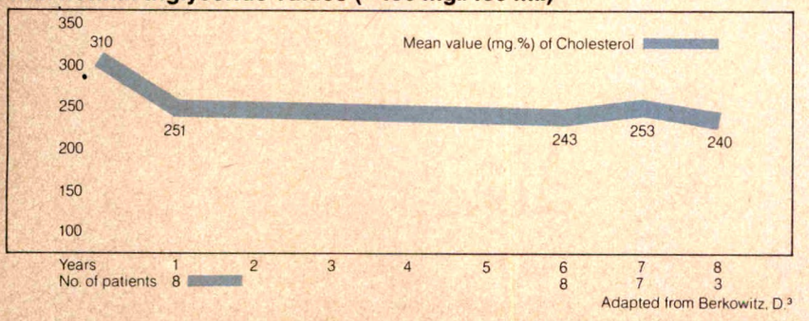
Atromid-S (clofibrate)—to help reduce elevated levels of cholesterol and/or triglycerides when diet alone is not enough

ATROMID-S as an adjunct to diet has a proved record of effectiveness in lowering elevations of both cholesterol *and* triglycerides. Lipid lowering is sustained as long as ATROMID-S treatment is uninterrupted. The drug is effective in a simple, well-accepted regimen that patients can stay with. Initial *and* maintenance dosage is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage. The lipid-lowering effect of ATROMID-S is usually noted during the first month of therapy. The higher the initial level, the greater the lipid reduction likely to occur. If response is inadequate after three months, the drug should be discontinued. However, if xanthoma tuberosum is present, treatment should be continued for longer periods (even up to one year), provided there is a reduction in the size and/or number of the xanthomas.

Significantly lowers cholesterol and triglycerides in patients with elevated serum levels of both lipids[3]



Significantly lowers elevated serum cholesterol levels in patients with normal triglyceride values (<150 mg./100 ml.)[3]



Adapted from Berkowitz, D.[3]

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Atromid-S® (clofibrate) helps control the lipid factor in your patient's profile

Initial and maintenance dosage: 2 Gm. daily (four capsules), in divided doses. Some patients may respond to a lower dosage.

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® (clofibrate)

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (Sf 20-400) rich in triglycerides than the low density lipoproteins (Sf 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur. During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These

effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage.
Maintenance: Same as for initial dosage.
Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S (clofibrate). The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

References: 1. Scheig, R.: Conn. Med. 39:71 (Feb.) 1975. **2.** Zelis, R.: Clinical Focus on Hyperlipidemia: Detection and Diagnosis, Ayerst Laboratories, 1975, p. 8. **3.** Berkowitz, D.: J.A.M.A. 218:1002 (Nov. 15) 1971.

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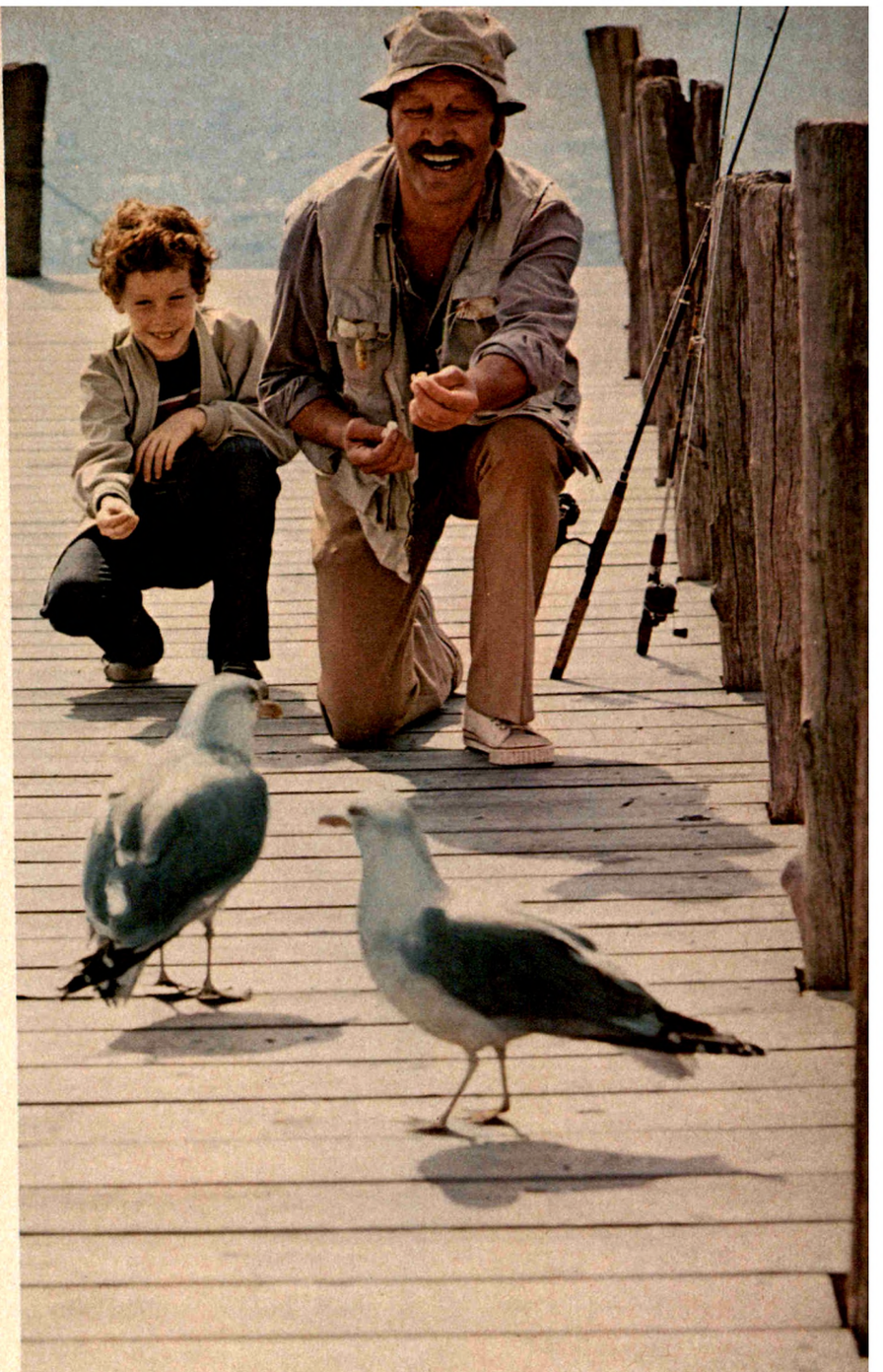

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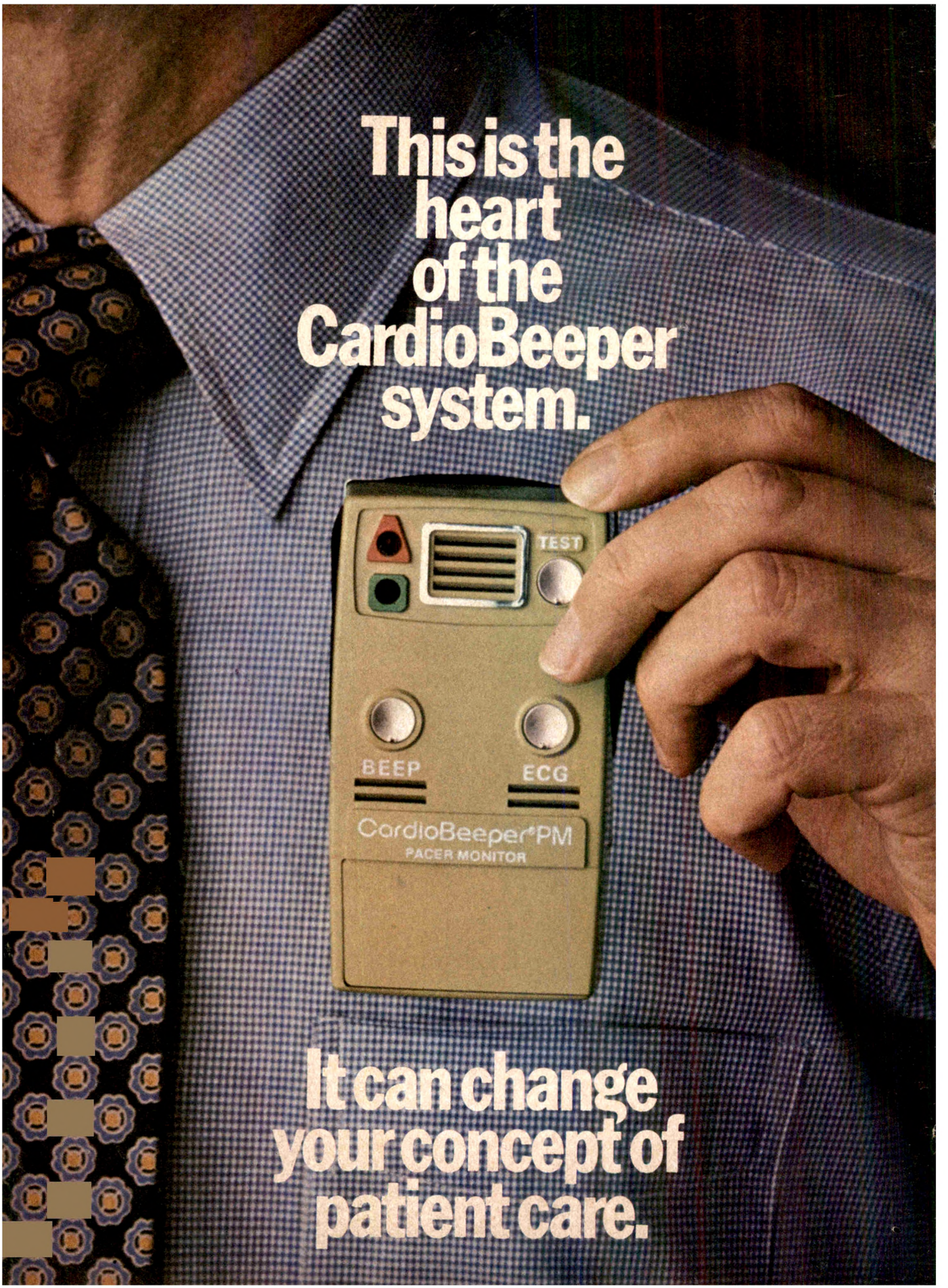
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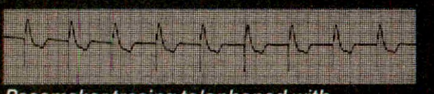

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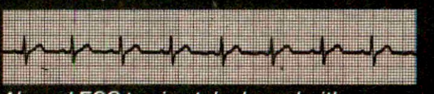

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The American Journal of CARDIOLOGY®

VOLUME 38

NUMBER 1

CLINICAL STUDIES

Echoventriculography in Acute Myocardial Infarction. III.

Clinical Correlations and Implication of the Noninfarcted Myocardium

MARKKU NIEMINEN, MD
JUHANI HEIKKILÄ, MD

Helsinki, Finland

Echoventriculography permits detection of regional abnormalities of left ventricular wall motion in acute myocardial infarction. Overall and regional performance of the left ventricle was related to the prognosis and clinical severity of acute transmural myocardial infarction in 30 patients. Although values for left ventricular size, ejection fraction and modified mean circumferential fiber shortening velocity were all abnormal ($P < 0.005$), they did not differ among 8 patients with uncomplicated infarction, 12 with moderate left ventricular failure and 10 with pulmonary edema or shock. In contrast, magnitude of the summed wall motion amplitudes from seven standard regions around the left ventricle decreased in parallel with ejection fraction ($P < 0.001$) and with clinical severity of infarction ($r = -0.79$, $P < 0.001$). Function of the healthy myocardium was hypercontractile in 40 percent of patients, but this occurred only in patients with uncomplicated or moderately severe infarction. In patients with severe pump failure the "uninvolved" myocardium did not manifest a hypercontractile or even normal response despite infusion of catecholamines (−21 percent; $r = -0.76$, $P < 0.001$). Four nonsurviving patients had the poorest ventricular function (as low as 10 percent of normal) as assessed by several segmental echocardiographic performance indexes. Performance of the noninfarcted myocardium therefore seems to have a role in deterioration of left ventricular pump function in acute myocardial infarction.

Abnormality of left ventricular contraction invariably occurs after acute myocardial infarction. Depending on the magnitude of the dysfunction, a spectrum of left ventricular failure develops, ranging from a clinically unrecognized condition to cardiogenic shock.[1] Until echocardiographic techniques were developed for analyzing local myocardial function in acute infarction,[2–4] and before the recent application of radionuclide angiography,[5,6] this basic physiologic disorder, left ventricular segmental dysfunction, could not be studied quantitatively.

In this study of 30 patients the clinical severity of myocardial infarction is related both to overall left ventricular pump performance and to

From the Cardiovascular Laboratory and the Intensive Care Unit, First Department of Medicine, University Central Hospital, Helsinki, Finland. This study was supported by the Paulo Foundation, Helsinki, Finland. Manuscript received September 17, 1975; revised manuscript received December 1, 1975, accepted December 3, 1975.

Address for reprints: Markku Nieminen, MD, Cardiovascular Laboratory, University Central Hospital, SF-00290 Helsinki 29, Finland.

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severity of segmental dysfunction as studied by quantitative echocardiography. Particular attention is focused on capacity of the noninfarcted segments to compensate for the acute reduction of pump function.

Patients and Methods

Patients

Thirty patients, 23 men and 7 women ranging in age from 30 to 68 years, were studied during the acute phase of their first myocardial infarction. With two exceptions they are the same patients reported on in Part I of our studies on echoventriculography in acute myocardial infarction.[4] All the patients were studied and treated in the intensive care unit; their relevant clinical findings are given in Table I. The diagnosis of acute infarction was based on the usual criteria of clinical features and electrocardiographic and serum enzyme changes.

On the basis of clinical severity of infarction, the patients were classified in three groups: *Group 1* consisted of 8 patients

TABLE I
Clinical and Echocardiographic Data in 30 Cases

Case no.	Sex	HR	BP	Site of MI	Arrhythmia	Drugs		Echocardiogram		
						Antiarrhythmic	Inotropic	LVEDV (ml)	ΣA (mm)	Ampl (mm)
					Group 1					
5	M	60	120	PL	...			385	43	10
6	M	65	105	PL	...	Lido 2, Pr 200	...	328	36	6
9	F	56	120	I	...	Lido 2	...	204	39	6
10	M	60	100	I	...	Lido 2, Proc 1.5	...	164	39	9
17	M	92	105	ExA	VF	Lido 2, Pr 200	...	184	34	15
27	M	75	100	PL	VP, VES	Lido 4	...	148	25	6
29	M	70	105	PL	...	Proc 1.5	...	225	38	10
38	M	65	105	PL	VF	Proc 3.0	...	148	32	10
					Group 2					
3	M	65	160	PL	...	Lido 2	...	328	21	9
11	M	100	110	AL	...	Lido 2	...	288	24	9
12	M	100	105	PL	...	Lido 2	Dig	356	26	7
19	F	74	150	PL	VT, VES	Lido 2.5	...	184	36	9
22	M	80	100	A	...	Lido 2	...	225	26	7
23	M	90	120	I	...	Lido 2, Pr 200	...	164	28	7
25	M	50	80	ExA	Brady	Proc 2.0	...	204	15	9
28	M	90	110	ExA	...	Lido 2, Proc 2.0	...	288	17	9
30	M	48	80	P	Brady, VES	Lido 2.5	...	138	32	6
33	F	92	110	PL	VF, Brady	Lido 2, Proc 2.0	...	249	27	8
34	M	80	120	ExA	VP	Lido 3, Pr 25 iv	...	328	23	10
37	M	60	110	PL	Brady	Lido 2	...	274	31	6
					Group 3					
8	M	80	110	AL	VF, VES	Lido 2	Dig	174	16	8
13*	M	90	80	ExA	VF	Lido 2	Dop 900	184	12	8
14	M	95	120	PL	...	Lido 3	...	225	23	7.5
16	F	75	130	AS	...		...	89	17	5
18*	F	105	80	ExA	VF	Lido 2	Dop 2000, Dig	165	16	6
20	F	80	100	PL	VES, AF	Lido 3	Dop 400, Dig	274	19	6
21	M	120	105	ExA	VT	Lido 2	Dop 250	385	6	7
24*	M	60	140	ExA	AF	Lido 2	Dop 150, Dig	356	21	8.5
32	F	120	80	PL	VP	...	...	148	25	10
39*	M	80	85	ExA	VF, VES	Lido 2	Dop 200	238	5	6
					Normal Values					
								118	46	A:5.2; P:8.3

* Patients who died.

A = anterior; AF = atrial fibrillation; Ampl = amplitude at the single noninfarcted region; BP = systolic blood pressure (mm Hg); Dig = digoxin; Dop = dopamine infusion (μg/min); ExA = extensive anterior; HR = heart rate (beats/min); IV = intravenously; I = inferior; L = lateral; Lido = lidocaine infusion (mg/min); LVEDV = left ventricular end-diastolic volume; MI = myocardial infarction; P = posterior; Pr = practolol (mg); Proc = procainamide (g); S = septal; ΣA = summed amplitudes (Fig. 1); VES = frequent ventricular extrasystoles; VF = ventricular fibrillation; VP = ventricular parasystole; VT = ventricular tachycardia.

with uncomplicated infarction who had no evidence of heart failure (MIRU class I[7]); the 12 patients in *group 2* had clinical signs of mild to moderate cardiac failure such as widespread pulmonary rales, loud third sound gallop (MIRU class II); and the 10 patients in *group 3* had severe infarction (MIRU classes III and IV) either complicated by frank pulmonary edema, serious cardiovascular failure or cardiogenic shock or progressing to death (4 patients). Inotropic medication was administered to only one patient in groups 1 and 2, whereas 7 of the 10 patients in group 3 required inotropic support with dopamine infusion (150 to 2,000 μg/min) or parenteral administration of digoxin, or both, at the time of the echographic studies (Table I). Most of the patients were treated with lidocaine infusion (1 to 4 mg/min) or were given procainamide orally (Table I). The beta adrenergic blocking drug practolol was used in four patients, two each in groups 1 and 2.

Echocardiographic Methods

The echocardiographic studies of the left ventricle were performed serially with a Picker Echoview II (Cleveland, Ohio) as earlier reported in detail.[3,4,8] In brief, overall pump function was assessed from end-diastolic and end-systolic volumes,[9,10] ejection fraction[9] and modified circumferential fiber shortening velocity (V_{CF}).[3,11] The regional function of the left ventricle was studied by multiaxis recordings from eight (AW1 to AW4 and PW1 to PW4) basic left ventricular regions (four anterior and four posterior) as obtained by four principal echocardiographic beam directions (Fig. 1). Because the lowest inferior region (PW4) was not recorded consistently, three posterior regions were included for the quantitative analyses. Technically, certain anterior wall areas may be difficult to recognize.[3,4,8] Furthermore, echocardiographs differ in ability to display clearly near field targets. We have found that this ability is at least acceptable with Smith Kline and Picker equipment.

Regional function was assessed in the seven segments (AW1 to AW4 andPW1 to PW3) by amplitude of the wall motion, taken from the onset of isovolumic contraction at the start of QRS complex to the peak of systole, and by velocity of the systolic motion. The latter was taken as a mean tangent to the systolic contour of the wall motion in the M-mode.[3] In cases of arrhythmia, only the ventricular contractions caused by supraventricular beats were accepted for analysis.

Sigma amplitude of the left ventricle was defined as the sum of excursions of the seven basic areas located around the

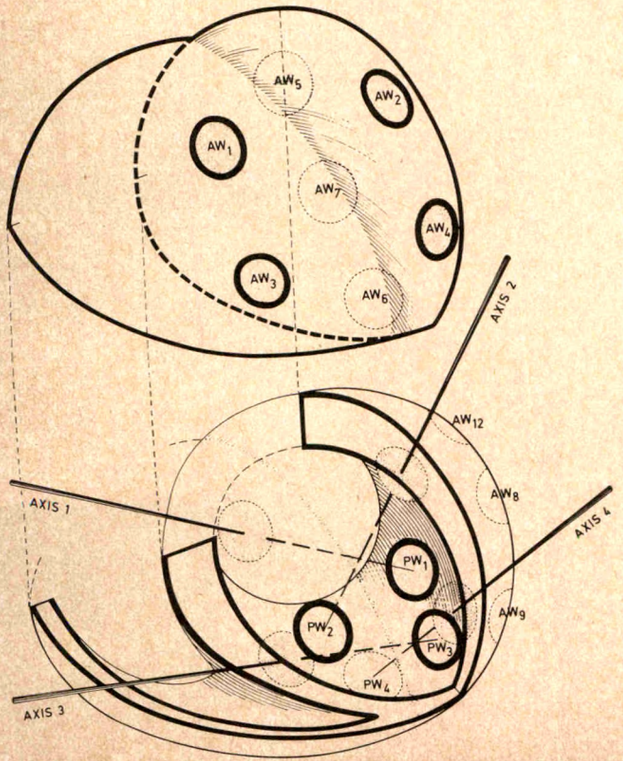

FIGURE 1. Schematic display of the seven standard regions used to study left ventricular segment function. Four anterior (AW1 to AW4) and three posteroinferior (PW1 to PW3) areas are explored[3] by the four basic echocardiographic beam directions (axis 1 to 4).

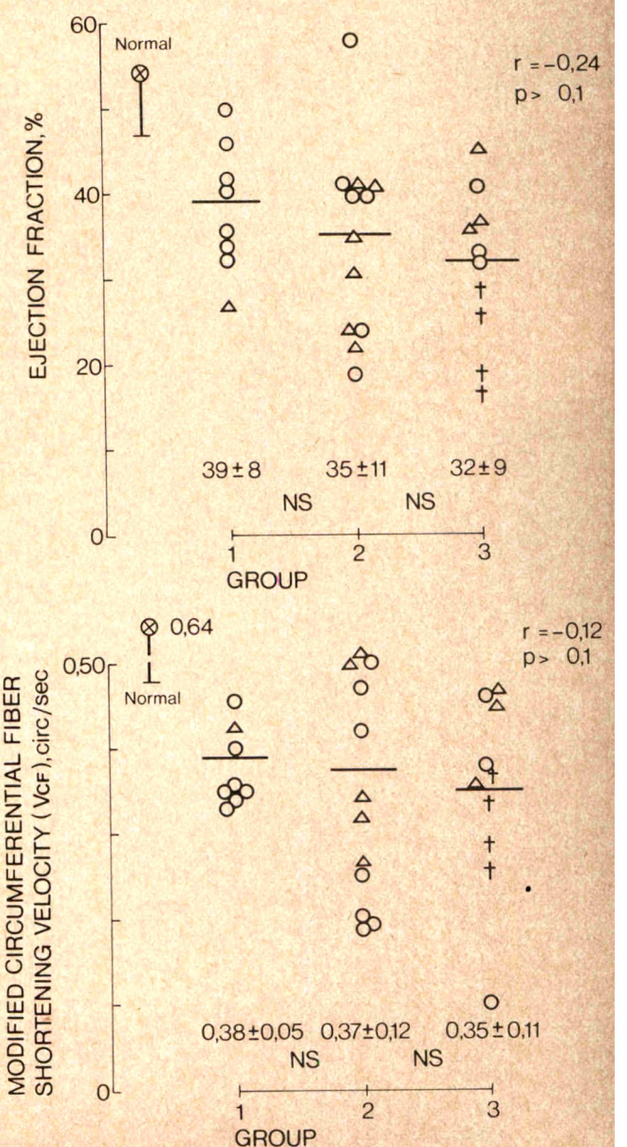

FIGURE 2. Relation of the echocardiographic ejection fraction and the modified circumferential fiber shortening velocity to the clinical severity of acute infarction in groups 1, 2 and 3. Circles = posteroinferior infarction; † = died; triangles = anterior infarction; circ = circumferences; NS = not significant.

entire left ventricle (PW1 to PW3 and AW1 to AW4, Fig. 1), and expressed as percent of the sum of the means of the corresponding seven systolic amplitudes of the normal left ventricle. The normal mean value[3] is 46 mm.

Sigma amplitude of the uninvolved regions was defined as the sum of the wall excursions of two to four uninvolved regions (belonging to some of the seven basic areas, Fig. 1), and expressed as percent of the sum of the normal wall motion amplitudes at the respective sites.[3] The number of sites subjected to analysis here varied somewhat since in a few cases the infarcted area clearly extended up to the "uninvolved" area. Particularly during the initial days of infarction ischemic zone asynergy surrounding the center of infarction may encompass large areas.[12,13] Events in such border areas do not indicate function of the noninfarcted segments.

Echocardiographic performance index was designed to combine both regional and overall pump function. It was defined as the sum of the percent sigma amplitudes from the seven basic regions plus the ejection fraction value.

In the 24 patients studied serially the echocardiograms taken on the 2nd or 3rd day were used for analysis since overall left ventricular function is poorest at that time.[8] The other six patients were studied only once, on the 1st or 2nd day of hospital care.

The statistical programs of the Hewlett-Packard 9810A calculator were applied to the data. The *t* test for means was used for statistical assessment of differences between groups, and the two-variable regression estimate was used for correlative studies of the different variables.

Results

Left Ventricular Pump Function

Although the left ventricular end-diastolic and end-systolic volumes, ejection fraction and circumferential fiber shortening velocity were abnormal ($P < 0.005$) in each clinical group, the groups did not differ from each other because of wide overlapping of values (Table I, Fig. 2). Ejection fraction correlated best (but not significantly) with clinical state (Fig. 2).

Regional Function

Infarcted region: Contractile function of the infarcted areas was drastically impaired in all patients, and there were no clear differences among the clinical groups. Excursion of the infarcted posterior wall was only 0.6 ± 2.0 mm (mean ± standard deviation) ($P < 0.001$), and anterior wall infarction resulted in paradoxical systolic motion of −3.6 ± 1.6 mm ($P < 0.001$). The velocity of the infarcted segments remained zero, with the exception of segments with posterior infarction in group 1 which manifested marked hypokinesia (7.3 ± 8.8 mm/sec).

Noninfarcted region: In the uninvolved posterior region the amplitude and velocity of systolic wall motion as determined from *single points* were within normal ranges in the three groups, except that values for posterior wall excursion were lower in group 3 than in group 2 (Table II). However, in the anterior wall function of the noninfarcted segments, as assessed from the segment AW1 to AW4 with the greatest amplitude, was similarly enhanced in all clinical groups (Table II).

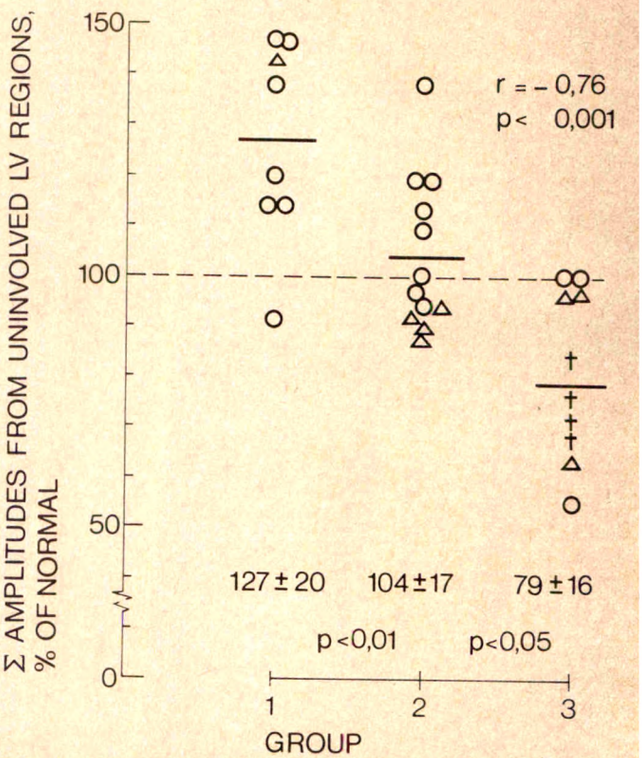

FIGURE 3. Sum of amplitudes from uninvolved left ventricular regions. Performance of the uninvolved myocardium measured from several segments correlated inversely with the severity of myocardial infarction. Supernormal function took place in patients with uncomplicated infarction (group 1), whereas in patients with a severe clinical course (group 3) the compensating capacity appeared remarkably inadequate. Symbols as in Figure 2.

TABLE II

Amplitude (mm) of the Wall Motion at the Single Noninfarcted Segment Showing the Most Vigorous Motion (means ± standard deviation)

	Posterior Wall			Anterior Wall		
	Amplitude	no.		Amplitude	no.	
Group 1	15	1		8.1 ± 2.0	7	
Group 2	8.8 ± 1.1	7	$P < 0.025$	7.4 ± 1.3	5	
Group 3	6.9 ± 1.3	7		7.8 ± 2.0	3	
Total	7.7 ± 1.5			7.8 ± 1.7		
Normal[3]	8.6 ± 2.0 (PW_2)	42		4.9 ± 1.6 (AW_1)	42	$P < 0.01$

AW = anterior wall segment; *P* = probability; PW = posterior wall segment.

Echocardiographic performance indexes: The regional function determined from multiple left ventricular segments correlated well with the clinical severity of infarction. The differences among clinical groups were significant (Fig. 3 to 5). Mean ventricular function assessed from the *summed noninfarcted segments* revealed hypercontractility in group 1 (27 percent increase) and to a lesser degree in group 2 (4 percent increase), and was greater than normal in 40 percent of all 30 patients (Fig. 3), but was reduced in group 3 (21 percent decrease) (Fig. 3; $r = -0.76$, $P < 0.001$). The reduction of "total" left ventricular segment function became evident in the assessment of the percent *sum of amplitudes from the seven regions.* Such function was decreased 22 percent in group 1, 45 percent in group 2 and 65 percent in group 3 (Table I; Fig. 4; $r = -0.79$, $P < 0.001$). The same sigma amplitude analysis also correlated with ejection fraction (Fig. 6; $r = 0.60$, $P < 0.001$). Combining the segment analysis and the ejection fraction (*echocardiographic performance index*) resulted in a similar ability to discriminate among clinical groups (Fig. 6; $r = -0.70$, $P < 0.001$).

Nonsurvivors

Four patients died in the hospital because of severe left ventricular failure. All had a large anterior infarction, with the serum lactic dehydrogenase peak levels exceeding 1,000 international units (IU)/liter. Their values for ejection fraction and regional contractile function were the lowest in group 3 (Fig. 2 and 4), and they were classified in a "risk" category of patients with an ejection fraction of less than 30 percent in association with regional contractile function of less than 50 percent. Two patients in group 2 had values within these limits but function of their uninvolved myocardium was

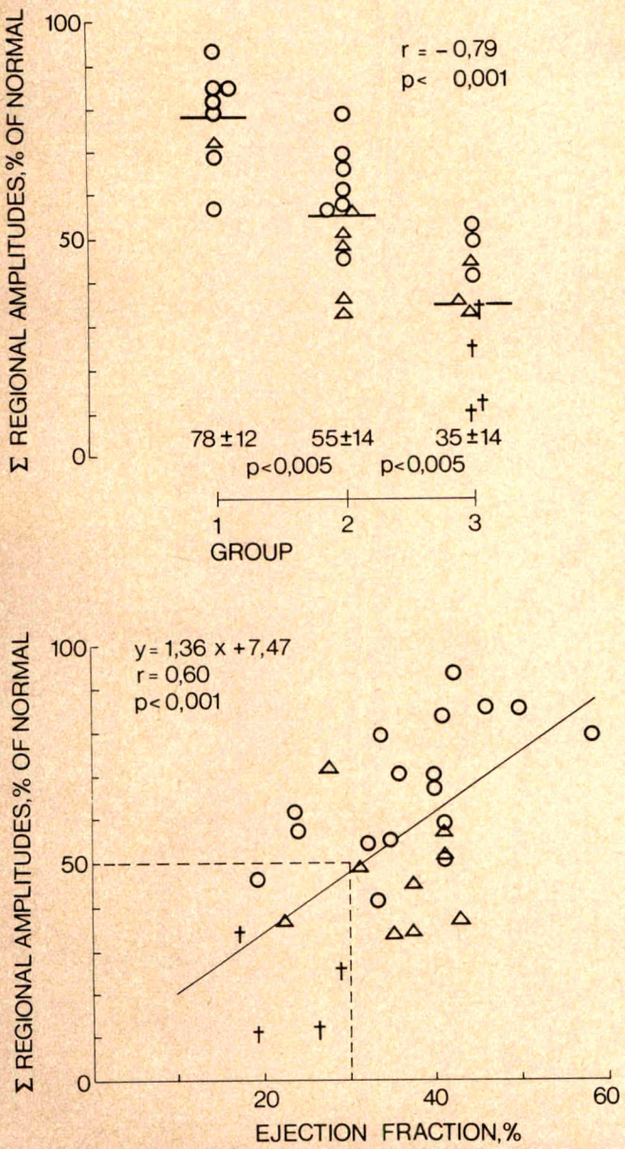

FIGURE 4. Summed regional wall motion amplitudes from the seven standard regions, including both the uninvolved and the infarcted segments. "Total" regional function always remains subnormal in acute infarction, and uninvolved regions fail to make full compensation even in cases of uncomplicated infarction. Their performance correlates significantly with the clinical severity of the infarction **(above)** (100 percent amplitude = normal segment function) and with the ejection fraction **(below).** Nonsurviving patients had the poorest segment function. Symbols as in Figure 2.

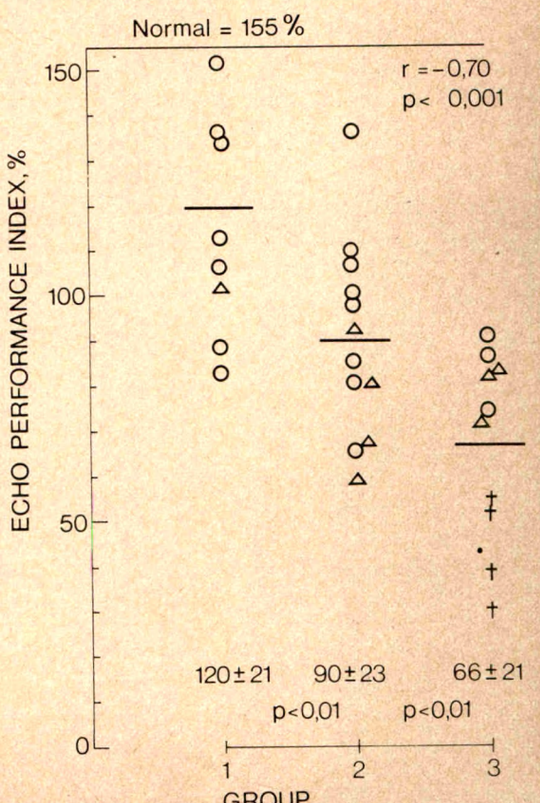

FIGURE 5. Echocardiographic performance index, combining the summed regional function and the ejection fraction, correlated with the clinical course. Reduction of the index by more than one third is seen in every patient in group 3, and the nonsurvivors again show the poorest values. Symbols as in Figure 2.

remarkably normal (93 and 94 percent, respectively, whereas that of the patients who died was depressed (Fig. 3). Thus, the echocardiographic performance index did not exceed one third of normal in any nonsurvivor and was higher in the surviving patients (Fig. 5). In these four nonsurviving patients the excursion amplitude of the noninfarcted segments remained subnormal (6.8 ± 1.0 mm; $P < 0.01$) even when measured from single points.

Laboratory Findings

Lactic dehydrogenase elevation (more than 190 IU/liter) was related to the clinical assessment of severity of the infarction: The mean values in clinical groups 1, 2 and 3 were, respectively, 581 ± 100, 754 ± 259 and 1117 ± 410 IU/liter ($r = 0.63$, $P < 0.001$). The catecholamine excretion value determined from 17 patients was highest on the 2nd day. These metanephrine values were similarly elevated in groups 1, 2 and 3 (7.3 ± 1.8, 9.6 ± 2.9 and 8.5 ± 1.3 μmol/liter, respectively; normal upper limit 4.1).

Discussion

Overall Left Ventricular Function

The echocardiographic measures of overall pump function were abnormal and values widely overlapped in each clinical group. This observation in acute myocardial infarction is in agreement with findings of others[14–16] and with the fact that direct hemodynamic investigations permit clear separation of patients only in cases of severe left ventricular failure and cardiogenic shock.[1,17–21]

Values for ejection fraction and circumferential fiber shortening velocity must be interpreted with great caution when derived from single beam echocardiograms because of the asynergic contraction of the infarcted ventricle. However, such systolic asynergy does not influence measurement of end-diastolic ventricular volume.[8,22] Further, the ventricular enlargement observed in acute infarction by echocardiography has recently been confirmed by scintiphotographic methods.[5,6] Our data thus indicate that a clinically uncomplicated infarction may mask an unstable hemodynamic state. Many clinical-hemodynamic studies[23] have shown that more than 50 percent of patients without clinical signs of left ventricular failure on admission have various manifestations of latent cardiac failure.

In our patients with severe myocardial infarction (group 3) two factors probably modified left ventricular volumes: there were relatively more women (4 of 10) than in the other patient groups, and 6 patients had infusions of dopamine during the study. Dopamine greatly decreases ventricular diameter and augments ejection fraction in acute myocardial infarction.[24] These factors, and perhaps patient selection to the intensive care unit within group 1, may explain why the echocardiographic index for overall pump performance in relation to the clinical severity of infarction had a weaker discriminating value than has been proposed by others.[15,25]

Regional Myocardial Performance

In contrast to the wide overlap among groups in the variables of overall pump function, the multiple regional function indexes differentiated the three clinical groups

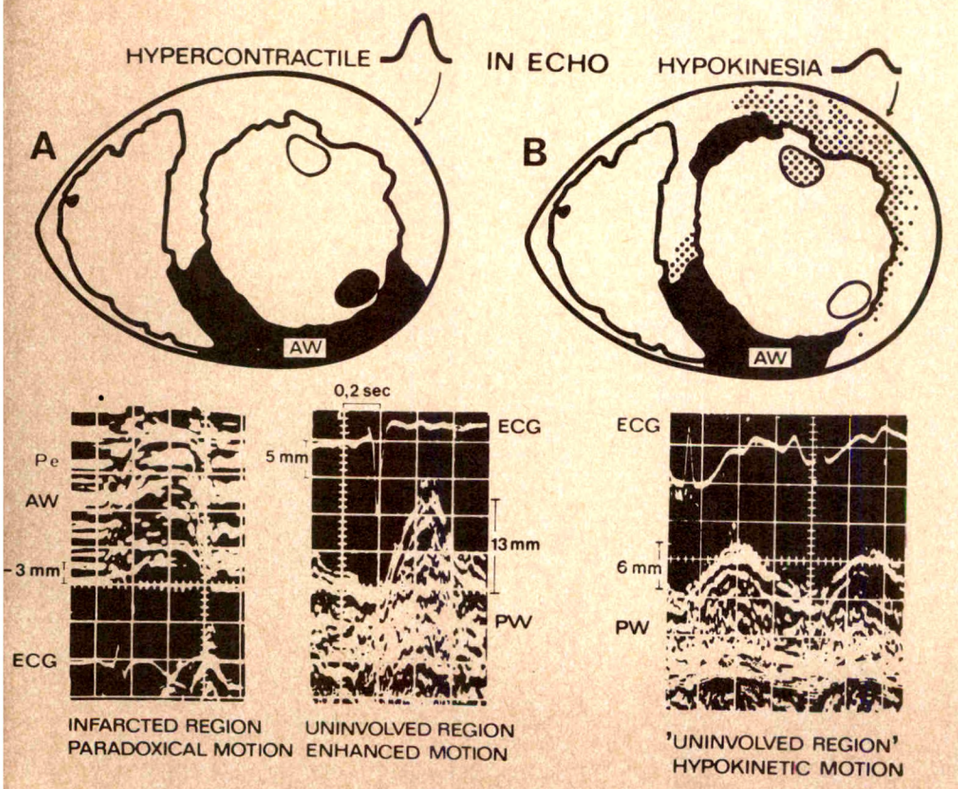

FIGURE 6. Performance of noninfarcted myocardium and pump failure. In acute myocardial infarction overall pump function is related not only to size of the infarct but also to performance of the noninfarcted muscle. **A,** healthy myocardium **(white areas)** is able to augment its systolic contraction proportionately to the size of the acute infarction **(black areas). B,** when the noninfarcted myocardium has been previously involved by fibrotic changes or its perfusion is restricted because of multiple coronary vessel disease, the normal compensatory action of the "uninvolved" segment **(dotted area)** fails to function, even under sympathoadrenergic stimulation. As a consequence, more serious total pump dysfunction results. AW = anterior wall; ECG = electrocardiogram; Pe = pericardium; PW = posterior wall.

from each other. Assessment of contractile performance at the seven standard regions of the left ventricle revealed an increasing abnormality of performance index in parallel with increasing severity of infarction and poorer prognosis.

This index encompasses both performance of the noninfarcted regions and extent of the infarct zone. Consequently, its correlation with the clinical course may be partly related to a greater frequency of extensive anterior wall infarction among patients with pump failure than among those with uncomplicated infarction (Table I).[4,26–27] Similarly, regional function at a given level of ejection fraction is better in posterior than in anterior infarction (Fig. 4). However, the contribution of infarct size to the performance index cannot be the sole explanation for our findings (Fig. 3). Function of the noninfarcted myocardium alone also correlated with the clinical group. Function of the noninfarcted regions was hypercontractile in patients with uncomplicated or moderately severe infarction but remained depressed in those with severe infarction and pump failure (group 3). This finding is in contrast to the suggestion of Mathey et al.[28] that even in severe infarction the noninfarcted myocardium compensates. Our direct data on segmental myocardial function in pump failure contradict their statement. Although Wharton et al.[29] reported severe deterioration of the noninfarcted posterior wall motion even in the absence of clinical evidence of left ventricular failure, their observation is difficult to explain because more epicardial than endocardial posterior wall echoes probably were recorded in that study.[29]

In experimental myocardial infarction there is good evidence that operation of the Frank-Starling mechanism becomes readily apparent.[12,30] As the size of the ischemic zone increases, healthy myocardium is able to respond with increasing systolic myocardial shortening. In human myocardial infarction this physiologic compensation operates too: Exaggerated normal function was seen in 40 percent of our series, but our data also indicate that the expected compensation often fails in patients whose condition progresses into pump failure. This dysfunction is probably due to preexisting myocardial changes or to triple vessel coronary artery disease supplying limited flow to the "uninvolved" regions (Fig. 6).[4,31–34] The demand for compensatory hyperfunction may also rapidly exhaust the enzyme systems of the myocardium.[35]

The observed hypokinetic function was documented despite the inotropic therapy given at the time of study to 7 of the 10 patients with severe infarction (group 3). Too, catecholamine excretion rates did not differ among the groups, so that the sympathoadrenergic drive was not smaller in the group in the poorest clinical condition.[21] Increased wall stress would also not provide an explanation since the end-diastolic volumes did not vary systematically (Table I).

Clinical Implications

The preceding data suggest that in hemodynamically severe myocardial infarction failure of the noninfarcted myocardium to compensate for the infarcted muscle mass is of importance. In agreement with this conclusion is an earlier observation that failure to increase stroke work significantly in response to the stimulus of intravenously administered norepinephrine indicates a poor prognosis.[1] We suggest that dysfunction of the "uninvolved" regions contributes significiantly to poor pump performance in severe myocardial infarction and is a factor to be considered when planning emergency cardiac surgery for cardiogenic shock.

Ventricular segment function of the healthy myocardium was supernormal in patients with uncomplicated infarction. In such patients the uninvolved areas probably consist of healthy myocardium. However, these segments seem to respond unnecessarily vigorously to sympathoadrenergic stimulation induced by pain, fear or ischemic damage.[36] In these patients particularly the use of beta adrenergic inhibition should be considered to protect the ischemic myocardium from the energy costs of overcontractile myocardial function.[12,13,24]

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Plasma Heparin Neutralizing Activity in Coronary Artery Disease

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Platelets contain heparin neutralizing activity that is released into plasma after platelet aggregation. Increased amounts of plasma heparin neutralizing activity were found in patients with acute myocardial infarction, unstable angina pectoris and stable arteriographically confirmed coronary artery disease. Plasma heparin neutralizing activity levels provide additional evidence for a role of platelet aggregation in coronary artery disease.

Several lines of evidence suggest a role for platelets in the development of coronary atherosclerosis and myocardial infarction. Enhanced platelet aggregation in response to suboptimal doses of aggregating agents such as adenosine diphosphate (ADP) and collagen have been found in patients with previous myocardial infarction[1,2] or angina pectoris.[3] Platelet hyperaggregability has also been demonstrated in patients with diabetes mellitus[4] or hyperlipidemias,[5] conditions associated with accelerated thrombotic vascular disease. Increased numbers of circulating platelet aggregates have been demonstrated in patients with transient ischemic attacks, myocardial infarction and acute peripheral vascular disease.[6] Platelet aggregates are also conspicuous in the small intramyocardial vessels of patients who die suddenly of myocardial infarction.[7,8] Animal experiments have demonstrated that transient ADP-induced platelet aggregates in the myocardial circulation of pigs cause ischemia, small infarcts and fatal arrhythmias.[9]

Platelets contain heparin neutralizing activity, which is found in the storage organelles of human platelets and is released into plasma during normal clotting and during in vitro aggregation with ADP, thrombin and collagen.[10–14] Utilizing a new assay to measure plasma heparin neutralizing activity derived from platelets, we present additional evidence for a role of platelet aggregation in coronary artery disease.

Material and Methods

Methods

Blood was collected from subjects by venipuncture after minimal venous stasis and anticoagulated with 1:10 volume of sodium citrate (3.8 percent). Platelet-poor plasma was prepared by centrifugation at 1,000 × *g* for 10 minutes at room temperature within 2 hours of sample collection; it had a platelet count of less than 8,000/mm^3. The plasma was separated and kept at −60° C in a Revco freezer until assay, usually within 2 weeks.

The assay system for measuring heparin neutralizing activity is a modification of the heparin-thrombin clotting time procedure of Harada and Zucker[11] and has been described in detail.[15] Briefly, each reaction mixture consists of 0.10 ml of test plasma, 0.10 ml of substrate plasma (pooled platelet-poor plasma collected from three to six normal donors) and 0.05 ml of the desired heparin dilution. This mixture is incubated for 1 minute at 37° C; then 0.05 ml of thrombin solution is added and the clotting time determined. Progressively higher concentrations of heparin are added to the reaction mixture to determine the minimal heparin concentration that reproducibly prolongs the clotting time beyond 20 seconds. A curve is then constructed with heparin concentration on the abscissa and clotting time on the ordinate, and the heparin concentration

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at which the curve crosses 20 seconds on the ordinate is taken as the heparin neutralizing activity value of the mixture. The heparin neutralizing activity of the substrate plasma is determined each day by plotting a curve for mixtures in which buffer substitutes for test plasma. This value is then subtracted from the heparin neutralizing activity values obtained for the experimental mixtures in order to eliminate the contribution of the substrate plasma. The final heparin neutralizing activity value for test plasma is expressed in units of heparin neutralized per milliliter of plasma. The larger the amount of heparin required to prolong the clotting time to more than 20 seconds, the greater the antiheparin activity of the test plasma.

A thrombin time determination with saline solution substituting for heparin in the reaction mixture is performed with each test plasma to ensure that the test plasma does not prolong the clotting time in the absence of heparin; such samples are discarded.

Diagnostic Categories

Acute myocardial infarction: Plasma heparin neutralizing activity was measured in 28 patients who manifested the characteristic chemical and electrocardiographic changes of acute myocardial infarction. Samples were drawn the morning after admission.

Unstable angina pectoris: Plasma heparin neutralizing activity was measured on the morning after admission in 32 patients admitted to a coronary care unit with unstable angina pectoris. These patients had crescendo angina of severe degree, usually in association with transient S-T or T wave changes in the electrocardiogram but without evolution to myocardial infarction and without serum enzyme changes.

Chronic coronary artery disease: Plasma heparin neutralizing activity was determined in 33 patients who entered the hospital for elective coronary bypass surgery. All patients in this group had severe angina pectoris but were in stable condition at the time of hospitalization. In each case the extent of coronary artery disease had been demonstrated by angiography.

Control population: Sixty healthy subjects, consisting of hospital personnel, office patients undergoing routine annual physical examinations and patients admitted to the hospital for elective orthopedic surgery, constituted a control population. The control group and the patient groups were comparable with respect to age and sex.

Statistical analysis: Heparin neutralizing activity values are expressed as mean units ± standard error of the mean. Results were analyzed for significance with the t test.[16]

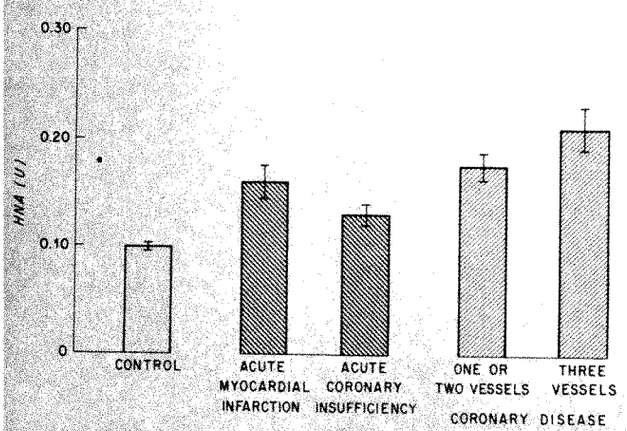

FIGURE 1. Mean plasma heparin neutralizing activity (HNA) in patients with acute myocardial infarction, acute coronary insufficiency and chronic coronary artery disease. All groups with coronary artery disease have a significant elevation of heparin neutralizing activity levels. U = units.

Results

Values for plasma heparin neutralizing activity in patients with coronary artery disease are shown in Figure 1. Activity was significantly elevated above control levels in patients with myocardial infarction (0.16 ± 0.014 [$P < 0.001$]) or acute coronary insufficiency (0.13 ± 0.009 [$P < 0.005$]). The difference between these two groups was not statistically significant. Patients with angiographically proved coronary artery disease had a mean plasma heparin neutralizing activity of 0.19 ± 0.011, which was significantly higher than control levels ($P < 0.001$). The 11 patients with one or two vessel coronary artery disease had a mean plasma heparin neutralizing activity of 0.17 ± 0.012; the corresponding value was 0.21 ± 0.019 in the 12 patients with three vessel disease. The difference between these two groups was not statistically significant.

Discussion

Our study, using a sensitive assay, confirms previous reports of elevated plasma heparin neutralizing activity levels in patients with myocardial infarction.[17,18] We have also demonstrated increased plasma heparin neutralizing activity in patients with acute coronary insufficiency or stable arteriographically confirmed atherosclerosis. Thus, increased plasma heparin neutralizing activity appears to be a characteristic feature of coronary artery disease irrespective of its clinical presentation. In contrast, we have found normal or reduced plasma heparin neutralizing activity in patients with a variety of other conditions, including acute leukemia, polycythemia vera, chronic myelogenous leukemia, essential thrombocythemia and idiopathic thrombocytopenic purpura.[15]

Heparin neutralizing activity and platelet aggregation: In in vitro systems the amount of heparin neutralizing activity liberated is closely related to the degree of platelet aggregation.[10–14] This relation has been confirmed in our assay system in which 30 percent platelet aggregation leads to a doubling of heparin neutralizing activity, and 100 percent aggregation leads to a threefold increase in heparin neutralizing activity released into plasma. Disruption of platelets by freeze-thawing also leads to a marked increase in heparin neutralizing activity released into plasma.[15]

It is likely that plasma heparin neutralizing activity also reflects the amount of in vivo platelet aggregation. For example, plasma heparin neutralizing activity closely parallels the degree of both experimental and clinical disseminated intravascular coagulation.[17,19] Patients with disseminated intravascular coagulation also manifested significant elevations of plasma heparin neutralizing activity in our assay system.[15] We have recently demonstrated that plasma heparin neutralizing activity is normal in patients with valvular heart disease

but is increased in patients with a prosthetic heart valve. This increase is presumably due to platelet aggregation on the prosthetic valve surface.[20] Elevated plasma heparin neutralizing activity may be related to the finding of platelet hypersensitivity to suboptimal amounts of aggregating agents. Both phenomena have been observed in myocardial infarction, angina pectoris and diabetes mellitus.[1-5,17,18,21]

Role of platelets in coronary artery disease: Many of the transient ischemic attacks in the cerebral and ophthalmic circulation appear to be directly due to evanescent platelet thrombi.[22,23] In a similar manner, circulating platelet aggregates may play a role in acute coronary insufficiency, particularly in young patients with myocardial infarction and normal coronary arteriograms. Evidence supporting this hypothesis has been presented by Salky and Dugdale.[2] Alternatively, platelets may aggregate secondarily at the site where arterial endothelial damage has already occurred. The release of vasoactive metabolites and hydrolytic enzymes such as serotonin and mucopolysaccharides after platelet aggregation may significantly contribute to the onset of coronary insufficiency and occlusion. Our finding of increased plasma heparin neutralizing activity in acute coronary insufficiency, myocardial infarction and stable angina pectoris provides further support for a role of platelets in the pathogenesis of coronary artery disease.

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Spectrum of Coronary Artery Disease in Idiopathic Hypertrophic Subaortic Stenosis

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The spectrum of coronary arterial involvement is described in 42 patients with hemodynamically proved idiopathic hypertrophic subaortic stenosis. Of nine patients with significant coronary arterial involvement, six had atheromatous disease and three had coronary arterial anomalies. The hemodynamic and clinical features of patients with coronary arterial involvement did not differ significantly from those of patients with normal coronary arteries. Neither the severity nor the character of the chest pain distinguished those patients with coronary disease. The diagnostic electrocardiographic features of myocardial infarction classically seen in patients with idiopathic hypertrophic subaortic stenosis were not present in the 9 patients with coronary arterial involvement but were found in 8 of the 33 patients with normal coronary arteries. The data demonstrate a significant incidence of coronary arterial involvement in patients with idiopathic hypertrophic subaortic stenosis after age 45 years.

Angina pectoris and a systolic murmur have been associated with the diagnosis of idiopathic hypertrophic subaortic stenosis since the latter was recognized in the 1950's. Cardiac catheterization studies have delineated the broad spectrum of the hemodynamic and angiographic features of this condition,[1–3] resulting in the recognition of many new cases. The use of noninvasive techniques such as carotid pulse tracings[4] and echocardiography[5–8] has improved selection of patients for cardiac catheterization and further contributed to the improved rate of recognition. Several reports[9–13] have described the clinical, hemodynamic, angiographic, electrocardiographic and pathologic manifestations of idiopathic hypertrophic subaortic stenosis but little mention has been made of associated coronary artery disease. Most of the early patients identified as having idiopathic hypertrophic subaortic stenosis were young, in the second and third decades of life, and several reports emphasized the presence of large normal coronary arteries.[9] Greater clinical awareness of the condition, the use of provocative maneuvers, better understanding of hemodynamic features (such as systolic anterior mitral valve movement) and use of noninvasive methods have since resulted in the diagnosis of many patients in the fourth to six decades of life who are more likely to have coexisting coronary artery disease. The early demonstration that large Q waves suggesting myocardial infarction were common in patients with idiopathic hypertrophic subaortic stenosis and normal coronary arteries further obscured the possible presence of coexisting coronary artery disease.[14–16]

This report describes the spectrum of coronary arterial involvement in 42 patients with hemodynamically proved idiopathic hypertrophic subaortic stenosis who underwent selective right and left coronary arteriographs. A significant incidence of atheromatous coronary artery disease and coronary anomalies was found in these patients.

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Material and Methods

Forty-two consecutive patients with idiopathic hypertrophic subaortic stenosis documented by complete right and left heart catheterization including selective right and left coronary arteriographs were studied. There were 28 men and 14 women with a mean age of 48 years (range 23 to 69). The indications for cardiac catheterization were a heart murmur (16 patients), chest pain (12 patients), chest pain and a heart murmur (7 patients), heart failure (5 patients) and syncope (2 patients). The diagnosis of idiopathic hypertrophic subaortic stenosis was established when, in addition to a left intraventricular pressure gradient at rest or after infusion of isoproterenol hydrochloride, one of the following was found: (1) a positive Brockenbrough response at rest or after infusion of isoproterenol, (2) angiographic demonstration of systolic anterior movement of the mitral valve, or (3) echocardiographic demonstration of systolic anterior movement of the mitral valve and septal hypertrophy. To avoid a misdiagnosis because of a spurious left ventricular gradient caused by catheter entrapment, the diagnosis was considered established only when the patient had a significant intraventricular pressure gradient (more than 35 mm Hg) and at least one additional criterion. Whenever possible, the intraventricular gradient was compared with data from pressure recordings from both the inflow and outflow tracts of the left ventricle.[1]

Left ventricular cineangiograms were obtained either in the biplane mode or in the single plane mode with right and left anterior oblique views. Multiple selective right and left coronary arteriograms were obtained with the Judkins technique in each patient; visualization of the coronary arteries from aortograms was not accepted as adequate. Mitral insufficiency was assessed from the angiograms on a scale of 0 to 4+. The clinical records were analyzed by an independent observer without knowledge of the hemodynamic and angiographic data.

The vectorcardiographic diagnosis of anterior or diaphragmatic myocardial infarction was made using the criteria of Starr et al.[17,18] The electrocardiographic diagnosis of anterior or diaphragmatic myocardial infarction was established using standard criteria.[19] The vectorcardiographic and electrocardiographic diagnosis of left ventricular hypertrophy was made using the criteria of Romhilt and associates.[20,21]

Statistical analysis of data was performed using a Student's t test for unpaired data and chi square analysis on an IBM 1130 computer.[22]

Results

Coronary arteriographic findings: Among the 42 patients with idiopathic hypertrophic subaortic stenosis who underwent selective coronary arteriography there were 6 with significant atheromatous coronary disease and 3 with coronary arterial anomalies (Table I). Among the six patients with atheromatous disease significant (75 percent or more) coronary stenosis was seen in one vessel in three patients, in two vessels in two patients, and in three vessels in one patient. No patient had involvement of the left main coronary artery. Four of the remaining 33 patients had insignificant atherosclerosis compromising less than 50 percent of one coronary lumen. Three patients had a coronary arterial anomalies (Fig. 1). In Patient 7 the left circumflex coronary artery arose from the ostium of the right coronary artery in the right coronary sinus. In Patient 8 all three coronary arteries arose from the right coronary sinus. In Patient 9 the right coronary artery arose from the left main coronary artery; no ostium was present in the right coronary sinus. Two additional patients had minor abnormalities involving displacement of the right coronary ostium to the superior portion of the right coronary sinus.

Correlation of arteriographic and clinical features: No significant difference in age, maximal left ventricular pressure gradient, presence of mitral insufficiency or incidence of angina, cardiac failure or syncope was seen when the 33 patients with normal coronary arteries were

TABLE I

Clinical, Hemodynamic and Angiographic Data in Nine Patients with Coronary Arterial Involvement

Case no.	Age (yr) & Sex	Angina	VCG, ECG*	Maximal Intraventricular Gradient (mm Hg)	MR	Post PVG	AMVM	Coronary Anomaly	Coronary Stenosis (%) RCA	LCA	LAD	LCF
1	48M	Severe	LVH	134†	3+	+	+	0	30	0	75	0
2	51M	Moderate, typical	LVH	154‡	2+	+	+	0	75	0	75	80
3	48M	Moderate	N	65‡	0	+	+	0	60	0	75	75
4	64M	None	LVH	146‡	2+	+	+	0	75	0	75	50
5	46M	Mild	N	40†	0	+	+	0	95	0	0	55
6	64M	Severe	LVH	90†	3+	+	+	0	50	0	75	0
7	45F	Moderate	N	52†	0	+	0	LCA arose from RCA	0	0	0	0
8	63F	Mild, atypical	LVH	114†	1+	+	0	RCA & LCA arose from RCS	0	0	0	0
9	52M	Moderate, typical	LVH	122†	0	+	+	RCA arose from LCA	0	0	0	0

* Vectorcardiographic (VCG) and electrocardiographic (ECG) features were tabulated only for the presence of anterior or diaphragmatic myocardial infarction and left ventricular hypertrophy (LVH).[14–18] In the absence of these criteria the tracings were termed normal (N). ST-T criteria were not used for this classification.

† Obtained at rest.

‡ Recorded after administration of isoproterenol.

AMVM = systolic anterior movement of mitral valve leaflet; LAD = left anterior descending coronary artery; LCA = left main coronary artery; LCF = left circumflex coronary artery; MR = mitral regurgitation; Post PVG = postextrasystolic accentuation of ventricular gradient (Brockenbrough response); RCA = right coronary artery; RCS = right coronary sinus.

compared with the 6 patients with atheromatous coronary disease (Table II). Likewise, left ventricular end-diastolic pressure, cardiac output and angiographic evidence of left ventricular hypertrophy did not differ significantly between the two groups. However, the great difference in size of the two patient groups reduces the value of these statistical comparisons. Analysis of the clinical and electrocardiographic data revealed no characteristics that identified patients with atheromatous coronary disease or anomalies. Four patients with coronary disease had typical angina, one had atypical angina and one had no angina. Two of the three patients with anomalous coronary arteries had typical angina and one had atypical angina. Of the 33 patients without coronary disease, 22 had typical angina, 3 had atypical angina and 8 had no angina.

Electrocardiographic and vectorcardiographic criteria for infarction were met in 8 of 33 patients with normal coronary arteries but in none of the patients with coronary disease. In three patients with normal coronary arteries and without a history of chest pain electrocardiographic criteria for diaphragmatic infarction were met. A history of previous myocardial infarction was present in 2 of 6 patients with coronary disease and in 5 of 33 without coronary disease. Patients with coronary disease were somewhat older (mean age 53 years, range 45 to 64) than patients with normal coronary arteries (mean age 46 years, range 23 to 69), but the difference was not significant. Significant atheromatous coronary disease was not found in any patient less than age 45 years but was present in 6 of the 25 patients aged 45 years or more.

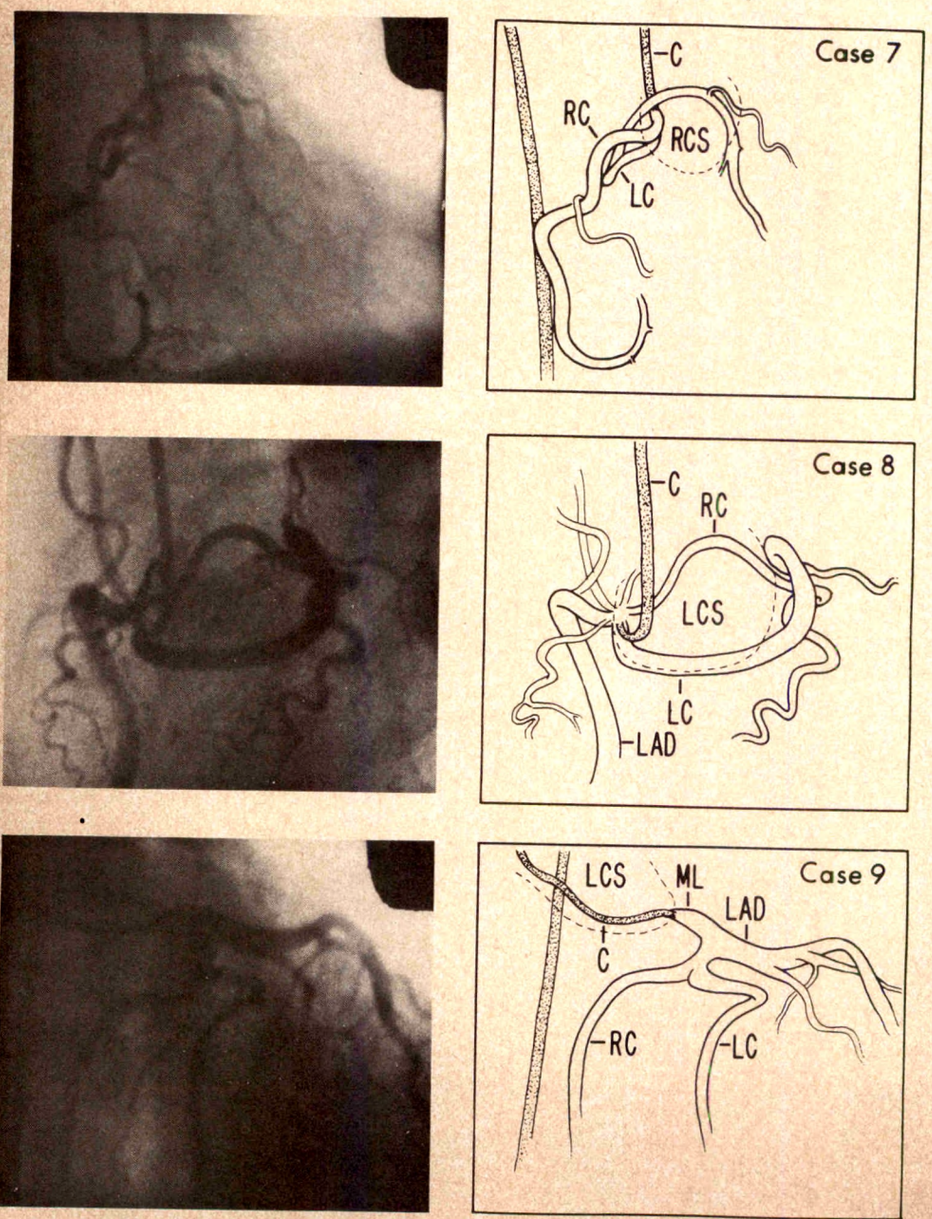

FIGURE 1. Representative cineangiographic frames **(left),** with explanatory diagrams from the three patients with coronary arterial anomalies. Films in Cases 7 and 9 are shown in the right anterior oblique view, in Case 8 in the left anterior oblique view. C = injection catheter; LAD = left anterior descending coronary artery; LC = left circumflex artery; LCS = left coronary sinus; ML = main left coronary artery; RC = right coronary artery; RCS = right coronary sinus.

TABLE II

Clinical and Hemodynamic Data in Patients With and Without Coronary Disease*

	Mean Age (yr)	Mean LV Gradient (mm Hg)	Incidence Rate (%)			
			MR	Angina	Cardiac Failure	Presyncope or Syncope
Normal coronary arteries (no. = 33)	46	95	36	76	33	45
Coronary artery disease (no. = 6)	53	104	67	83	17	33

* There was no significant difference between groups in any of the six variables ($P > 0.05$, Student's paired t test).
LV gradient = peak to peak maximal left ventricular gradient; MR = mitral regurgitation.

Discussion

Coexisting coronary artery disease: The presence of coronary arterial involvement has received little attention in the previously reported series of patients with idiopathic hypertrophic subaortic stenosis.[9–13] Several recent texts make no mention of the possible coexistence of these conditions.[23,24] Three previous reports[14–16] described a total of seven patients with electrographic features diagnostic of myocardial infarction and normal coronary arteries. These patients ranged from 19 to 40 years in age; only one was older than 30 years. These early reports emphasized the common occurrence of electrocardiographic changes diagnostic of infarction in young patients with idiopathic hypertrophic subaortic stenosis and normal coronary arteries. Gulotta et al.[25] reported on 10 patients with disabling angina pectoris who were found at cardiac catheterization to have idiopathic hypertrophic subaortic stenosis and significant coronary artery disease. Eight of these patients had a history of myocardial infarction and three had electrocardiographic evidence of infarction. All of these patients were over age 45 years (mean 52 years, range 46 to 69). The authors could identify no clinical or hemodynamic features to distinguish the patients with coronary artery disease. Epstein et al.[26] in a recent review of asymmetric septal hypertrophy reported that pathologic examination of 20 patients with subaortic stenosis revealed 7 with greater than 50 percent coronary arterial stenosis; however, these workers did not present clinical or hemodynamic correlations or list the number of patients with significant (more than 75 percent) coronary stenosis. In another 55 year old patient with idiopathic hypertrophic subaortic stenosis and subendocardial infarction,[27] a significant right coronary lesion was demonstrated at catheterization and the patient underwent a septal myectomy and a right aortocoronary bypass with complete amelioration of the anginal syndrome.

Coronary anomalies: Anomalies of the coronary system are rare[28] and no previous reference to their association with idiopathic hypertrophic subaortic stenosis has been found.[28,29] The exact incidence of coronary anomalies is difficult to ascertain, but the finding of three instances in our 42 patients is clearly unusual. The possibility of a developmental relation between the coronary anomaly and idiopathic hypertrophic subaortic stenosis may be delineated as more coronary arteriographic data become available. The recognition of idiopathic hypertrophic subaortic stenosis in stillborns shows that it can occur at a very early age. Since patients with coronary anomalies are affected from early development one may speculate that there is a causal relation between the two diseases. However, the relation of the coronary anomaly to the development of idiopathic hypertrophic subaortic stenosis is unknown.

Clinical implications: Our data reveal a 15 percent incidence rate of atheromatous coronary disease in idiopathic hypertrophic subaortic stenosis. The relation of age to the incidence of coronary stenosis is demonstrated by the 24 percent incidence rate of coronary involvement in patients more than 45 years of age as compared with the 0 percent incidence rate in young patients. Insignificant coronary stenosis (less than 75 percent) was found in three additional patients and may have contributed to their anginal pain. Coronary lesions with less than 75 percent stenosis may not be hemodynamically significant in patients with a normal myocardium. However, one may speculate that such lesions may result in ischemia, particularly during stress, in patients with idiopathic hypertrophic subaortic stenosis, who have a greatly thickened left ventricular wall and papillary muscles and increased myocardial oxygen consumption as a result of the intraventricular pressure gradient and mitral insufficiency. Therefore, the true contribution of occlusive coronary disease to the anginal pain in patients with idiopathic hypertrophic subaortic stenosis may be significantly greater than is currently appreciated although, this hypothesis cannot be tested with available data.

The clinical response to propranolol therapy in many patients with idiopathic hypertrophic subaortic stenosis may be partly related to the reduction in ischemic pain caused by atheromatous coronary disease.[30] The selection of appropriate surgical or medical therapy would be facilitated by a knowledge of the underlying coronary arterial anatomy in these patients. Coronary lesions may be bypassed as part of the operative procedure, and the failure to correct associated coronary lesions may have been responsible for the lack of response of some patients to septal myectomy. A recent report[31] of postoperative results in patients with idiopathic hypertro-

phic subaortic stenosis shows that in 18 percent of patients with severe intraventricular obstruction angina was not corrected by surgery; this figure compares well with our finding of a 15 percent incidence rate of atheromatous coronary disease in this condition. The incidence of coronary disease in our 42 patients suggests that selection and evaluation of medical or surgical therapy could be facilitated by knowledge of the coronary anatomy, particularly in patients over age 45.

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Effects of Excess Glucose and Insulin on Glycolytic Metabolism During Experimental Myocardial Ischemia

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The selective metabolic effects of glucose and insulin were tested in an intact working swine heart preparation. Supplements of glucose (26.6 millimolar [mM] and insulin (0.025 units/ml) were provided to 18 hearts, 9 control hearts (coronary flow 151 ml/min) and 9 hearts rendered globally ischemic (coronary flow reduced from 167 to 85 ml/min). These hearts were compared with 14 additional hearts (6 control and 8 ischemic) given no supplements (glucose 8.6 mM, no excess insulin). In hearts without supplements, ischemia significantly decreased mechanical performance, myocardial oxygen consumption, fatty acid oxidation and tissue high energy phosphate stores. Glucose consumption was reduced from 133 micromoles (μmol)/hr per g (before ischemia) to 58 μmol/hr per g ($P < 0.05$), presumably from inhibition at glyceraldehyde-3-phosphate dehydrogenase. Data for control hearts with excess glucose and insulin were similar to data in control hearts without supplements except that glucose consumption and glycolytic flux were increased. Ischemia in treated hearts, as compared with untreated ischemic hearts, effected similar significant decreases in myocardial oxygen consumption, fatty acid oxidation and high energy phosphate stores and resulted in greater reductions in mechanical performance and in 10 minutes' less average survival time. Glucose consumption was reduced from 483 (before ischemia) to 242 μmol/hr per g ($P < 0.005$) and inhibition at glyceraldehyde-3-phosphate dehydrogenase was again noted. Thus, excess carbohydrate and insulin hormone, when infused directly into the ischemic myocardium, did not provide an efficacious increase in either glycolytic flux or energy production. These findings suggest that an alternative explanation for the reported efficacy of glucose-insulin-potassium infusions must be sought.

In 1961, Sodi-Pallares[1] described an early treatment for myocardial ischemia that consisted of an intravenous infusion of a buffered "polarizing" solution containing excess glucose, insulin and potassium. The rationale for this therapy was to replace intracellular potassium lost during myocardial ischemia and to accelerate anaerobic glycolysis through the provision of additional glucose and insulin. Initial clinical studies[2–5] were encouraging, with a reported lessening of the frequency, duration and severity of symptoms, dysrhythmias and other electrocardiographic changes, congestive heart failure, fever and shock. However, confirmation of these early results has proved difficult and results of most other clinical trials have been disappointing.[6–9] Brachfeld[10] recently reviewed the wide variance in conclusions of these studies and suggested several possible means of explaining the discrepancies, one of the foremost being defining the metabolic mechanisms and measuring the changes in metabolic pathways that occur when components of the solution are administered singly and in combination. Maroko et al.,[11] who demonstrated an efficacious effect of both glucose-insulin-potassium and glucose alone in a canine preparation with coronary occlusion, postulated that the major benefits were primarily from glucose rather

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than potassium through an increase in energy production from enhanced glycolysis. Although they did not measure glycolytic flux rates and products of oxidative phosphorylation, they demonstrated histochemically greater preservations in cell integrity, greater stores of intracellular glycogen and less total depletion of myocardial creatine phosphokinase in glucose-treated hearts. Opie et al.,[12] studying the metabolic changes within 1 hour of inducing small infarcts in baboons, noted improvements in energy production with glucose and insulin but for reasons other than increased glycolysis, which they could not demonstrate in infarcted zones. Rovetto et al.[13] found neither protection nor increased glycolysis in ischemic rat hearts treated with gluclose and insulin, but they were using an isolated model system in a species far removed from man at severe levels of coronary flow restriction.

Such disparities underscore the lack of understanding concerning carbohydrate utilization in ischemic heart muscle, the extent of energy production possible from anaerobic glycolysis and the benefits that may derive from such therapy. This study was designed to evaluate the mechanisms of regulation in glucose consumption during myocardial ischemia using in situ working swine hearts perfused with whole blood. Availability of glucose and insulin was maximized in selected groups of hearts to enhance separation of metabolic changes. Free fatty acid was also provided at comparable levels in each group to act as additional substrate. Total reductions in coronary flow, which were controlled and regulated extracorporeally, were kept small, as judged by previous performance responses, to avoid irreversible tissue damage that could obscure the potential for biologic responsiveness. Global ischemia was induced to improve the homogeneity of blood and tissue samplings from ischemic hearts.

Methods

Thirty-two swine of either sex, weighing 32.7 to 56.8 kg (average 42.0 kg), were studied after anesthesia with sodium pentobarbital (35 mg/kg body weight) and the establishment of controlled positive pressure ventilation using 100 percent oxygen. Frequent determinations of the animal's arterial pH, partial pressures of oxygen and carbon dioxide and carbon dioxide combining power were obtained throughout each study to assure adequacy of ventilation and acid-base balance.

Experimental Preparation

Whole heart ischemia in the intact working swine heart preparation has been described previously.[14] After bilateral thoracotomy with transsternotomy, right heart bypass from the venae cavae to the pulmonary artery was constructed with antegrade control of systemic cardiac output maintained by a high-flow Sarns roller pump (no. 6002). The circuit was primed with 1 to 2 liters of heparinized fresh whole blood from a donor pig. Total coronary perfusion was established using a recirculation closed loop from the right ventricular drainage sump to the cannulated left and right coronary arteries at flow rates controlled by a low-flow Sarns perfusion pump (no. 6050). Coronary perfusate was reoxygenated at 37.5°C by a Bentley blood oxygenator (no. Q-130) with a gas mixture of 97 percent oxygen and 3 percent carbon dioxide. Aliquots of perfusate were obtained at 10 minute intervals during the perfusion studies from side ports just distal to the right ventricular sump and proximal to the coronary cannulas for sampling arteriovenous differences of oxygen and metabolites across the myocardium.

Preparation of Coronary Perfusate

Central coronary loop volume in each study averaged 1,500 ml. Coronary perfusate consisted of donor pig erythrocytes, washed twice with physiologic saline solution and twice with Krebs-Henseleit bicarbonate buffer within 24 hours of the experiment, combined on the day of use with buffer to a final average hemoglobin concentration of 8.0 ± 0.1 g/100 ml (mean ± standard error of the mean). Final concentration of salts in the buffered (pH 7.40) medium in millimolar (mM) were: sodium chloride 118; potassium chloride 4.7; calcium chloride 5; magnesium sulfate 1.2; potassium dihydrogen phosphate 1.2; calcium ethylenediaminetetraacetic acid 0.5, and sodium bicarbonate 25, as described elsewhere.[15]

Palmitic acid (Fisher Scientific Company) with tracer quantities (70 microcuries[μCi]) of uniformly labeled carbon 14 (U-^{14}C) palmitate (New England Nuclear Corporation) was combined with albumin by adding the fatty acid to an aqueous solution of sodium carbonate. Absolute ethanol was added with warming until the fatty acid dissolved, and the ethanol was then evaporated from the resulting soap solution by further warming on a hot plate. The soap was redissolved in a small volume of warm saline solution and combined slowly with 10 percent albumin (Pentex, fraction V). The fatty acid-albumin solution was dialyzed overnight against Krebs-Henseleit buffer and added to the washed red blood cells on the day of study to give final albumin concentrations of 4 g/100 ml and free fatty acid levels of 1.26 ± 0.04 mM.

In 14 animals, arterial glucose concentration in the coronary loop averaged 8.6 ± 0.8 mM (154 mg/100 ml); in these hearts, no insulin was added to the perfusate. In the remaining 18 swine, coronary perfusate was enriched approximately threefold with excess glucose (loop concentration 26.6 ± 1.3 mM [478 mg/100 ml]), in addition to regular crystalline zinc insulin (0.025 unit/ml).

Measurement of Hemodynamic Performance of the Heart

Heart rate (atrially paced using a Medtronic 5880A pacemaker on demand mode), coronary blood flow, cardiac index (determined from the flow rate of the right heart bypass perfusion pump normalized by animal weight in kilograms), aortic peak and average systolic pressures, left ventricular end-diastolic pressure and pressure time per minute were determined at 10 minute intervals during control perfusions and at 5 to 10 minute intervals during ischemic perfusions. Pressures were measured from Statham P23db pressure transducers connected to short fluid-filled catheters inserted into the central aorta and left ventricle. Pressure time per minute was calculated from the formula:

Pressure time per minute (mm Hg · sec/min) = average aortic systolic pressure (mm Hg) × ejection time (sec) × heart rate (beats/min)

Metabolic Determinations

Oxygen consumption was calculated for both hemoglobin and plasma transport since arterial oxygen tension in the coronary circuit routinely exceeded 500 mm Hg. Measurement of perfusate hemoglobin, arterial and venous oxygen tension (PO_2) and hemoglobin oxygen saturation levels were obtained using an Instrumentation Laboratory blood gas analyzer, model 313, and co-oximeter, model 182, respectively. Myo-

cardial oxygen consumption ($M\dot{V}O_2$) was calculated from the following expressions:

Via hemoglobin transport

$M\dot{V}O_2$ (mmol/hr per g dry weight) = 1.39 × coronary flow rate (ml/hr) × hemoglobin concentration (g/100 ml) × arterial − venous oxygen saturation (Δ%)/22.4 (ml/mmol) × dry weight of heart (g)

Via plasma transport

$M\dot{V}O_2$ (mmol/hr per g dry weight) = arterial − venous oxygen tension (Δ mm Hg) × solubility of oxygen at 37° C (ml/ml H_2O) × coronary flow (ml/hr)/22.4 (ml/mmol) × dry weight of heart (g) × 760 (mm Hg)

$M\dot{V}O_2$ values separately calculated for hemoglobin transport and plasma transport were summated for total $M\dot{V}O_2$.

Uptake of fatty acids was estimated from the clearance of [U-^{14}C] palmitate from the labeled perfusate. Samples of arterial and venous blood were collected at 10 or 5 minute intervals and centrifuged, and an aliquot of serum was used for determining radioactivity due to ^{14}C-palmitate. After removal of carbon-14 dioxide ($^{14}CO_2$), more than 90 percent of the serum radioactivity was extractable by chloroform of Doles reagent and was therefore present as long-chain fatty acids. In separate studies it had been determined that the radioactivity present in the aqueous phase after fatty acid extraction represented no more than 8 percent of the remaining radioactivity even after 2 hours of perfusion and no more than 2 percent of the radioactivity added initially as U-^{14}C palmitate. A change in the amount of aqueous soluble radioactivity between arterial and venous samples could not be detected. The total fatty acid content of serum was determined by the colorimetric procedure of Duncombe.[16] Fatty acid uptake was calculated as:

μmol FFA/hr per g dry weight = arteriovenous [U-^{14}C] FFA (counts/min per ml) × coronary flow (ml/hr)/1/2 [arterial + venous specific activity of ^{14}C-FFA (counts/min per μmol FFA)] × dry weight of heart (g) where FFA = free fatty acid.

Total coronary flow was used since the arteriovenous differences of labeled fatty acids from the red blood cell fraction were the same as for serum.

The rate of fatty acid oxidation was estimated by measuring $^{14}CO_2$ production from [U-^{14}C] palmitate. Blood samples for CO_2 analysis were collected under heptane. One milliliter of whole blood was transferred to a 25 ml Erlenmyer flask containing 1.0 ml of 12N hydrogen sulfate in the bottom of the flask and 0.4 ml of hyamine hydroxide in a plastic central bucket suspended from the stopper. After the blood and acid were mixed, the samples were allowed to stand for 2 hours before the buckets were removed, placed in 10 ml of toluene scintillator and counted in a Beckman 150 liquid scintillation counter. Corrections for quenching were made by the channels-ratio method.[17] Fatty acid oxidation was calculated as:

μmol FFA/hr per g dry weight = venous − arterial-$^{14}CO_2$ (counts/min per ml) × coronary flow (ml/hr)/1/2 [arterial + venous specific activity of ^{14}C-FFA (counts per min/μmol FFA)] × dry weight of heart (g)

The rate of glucose utilization was estimated by measuring the disappearance of glucose from the coronary loop blood over the course of the perfusion run at either 5 or 10 minute intervals. Serum glucose was measured on a Technicon Auto Analyzer. Comparative estimations by the glucose oxidase method[18] in preliminary studies were in near perfect agreement with measurements from the Auto Analyzer, excluding the presence of significant levels of other reducing substances. The difference in perfusate glucose levels between consecutive time intervals was obtained and multiplied by the coronary loop blood volume at that time to calculate the glucose consumption, expressed as μmol glucose/hr per dry weight of heart (g).

Transmural sections of ventricular myocardium were immediately removed at the conclusion of each perfusion study and frozen between blocks of aluminum cooled in liquid nitrogen. The frozen tissue was later powdered, and aliquots of this were obtained for determination of tissue glycogen content.[19] Additional samples of powder were extracted in 6 percent perchloric acid, and the buffered supernatant was used to determine tissue concentrations of creatine phosphate and adenosine triphosphate (ATP), diphosphate (ADP), and monophosphate (AMP), lactate, pyruvate, glucose-6-phosphate, fructose-1,6-diphosphate, triose phosphates and α glycerol phosphate. Creatine phosphate and ATP were assayed by the hexokinase, glucose-6-phosphate dehydrogenase procedure.[20] ADP and AMP were determined after the method of Adam[21]; tissue lactate, glucose-6-phosphate and glycerol phosphate by the procedure of Hohorst[22–24]; pyruvate by the method of Bucher et al.[25] and fructose-1,6-diphosphate and trioses (glyceraldehyde phosphate and dihydroxyacetone phosphate) from the methods of Bucher the Hohorst.[26]

Experimental Protocol

The general scheme of our studies was to quantitate in separate experiments the levels of glucose consumption and glycolysis present in both ischemic and nonischemic swine hearts and to evaluate the changes that occur as a function of augmented glucose and insulin availability. Fatty acid availability to the myocardium was also provided at comparable levels in all groups. Control coronary flow levels, determined initially by measuring right ventricular drainage, were maintained for 60 minutes in 15 hearts (9 perfused with high concentrations of glucose and insulin and 6 without substrate or hormone augmentation). In 17 hearts (9 perfused with excess glucose and insulin and 8 without enrichment), normal coronary perfusion was maintained for 20 minutes and then critically restricted over a 10 minute period (respective reductions in total flow of 49 and 46 percent). The initial 20 minute period of control perfusions in these hearts permitted adequate mixing of the various ingredients in the coronary central loop volume and allowed for equilibration of intracellular and extracellular ^{14}C-palmitate together with achievement of steady state production rates of $^{14}CO_2$ from oxidation of ^{14}C-palmitate. Gradual rather than precipitous reductions in coronary flow levels were necessary since in this preparation sudden large reductions in flow almost invariably resulted in ventricular fibrillation. Mechanical and metabolic measurements were obtained for control and ischemic states and compared in relation to both coronary flow and glucose and insulin enrichment. Comparisons were made using paired and unpaired Student t tests with statistical significance defined for probability values of less than 5 percent. All data were expressed per gram dry weight of ventricular myocardium.

Results

Nonischemic hearts with and without excess glucose and insulin supplements: Control information for both groups of nonischemic hearts are shown in Table I. There were no significant differences in any of the controlled hemodynamic variables throughout the course of the perfusion trials in either group or between groups although cardiac output was adjusted

TABLE I

Control Data on Heart Groups With and Without Excess Glucose and Insulin Supplements

	Body Weight (kg)	Ventricular Weight (g dry)	Coronary Perfusate Hemoglobin Concentration (g/100 ml)	Heart Rate (beats/min)	Cardiac Index (ml/min per kg)	Peak Aortic Pressure (mm Hg)
Nonischemic hearts						
Without excess G/I (no. = 6)	40.0 ±2.3	28.6 ±1.6	7.8 ±0.3	104.3 ±0.3	42.5 ±0.6	93.3 ±0.8
With excess G/I (no. = 9)	42.6 ±2.8	29.4 ±1.3	8.0 ±0.4	103.7 ±0.8	38.2 ±1.1	92.0 ±0.7
Ischemic hearts						
Without excess G/I (no. = 8)	42.1 ±2.7	28.2 ±1.2	8.3 ±0.2	101.0 ±0.7	36.0 ±0.7	94.9 ±0.8
With excess G/I (no. = 9)	43.4 ±2.5	31.5 ±2.3	7.9 ±0.2	105.5 ±0.3	42.8 ±2.0	88.0 ±2.4

All data are given as mean data for the perfusion trial ± 1 standard error of the mean.
G/I = glucose and insulin.

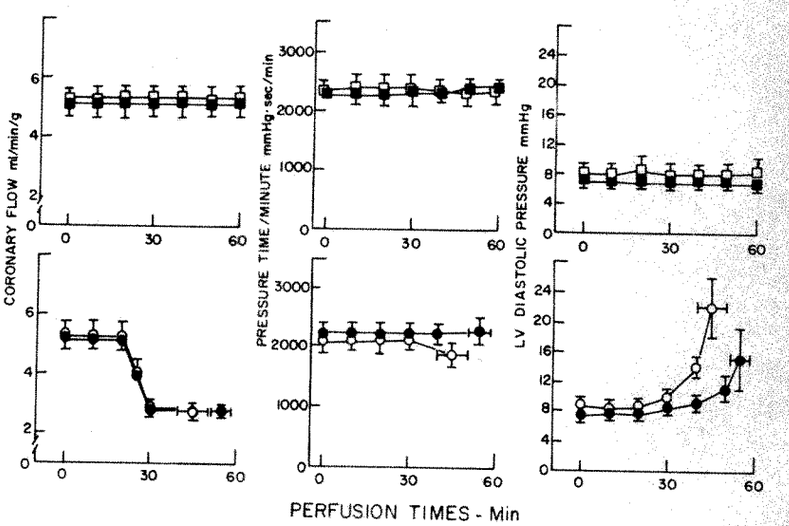

FIGURE 1. Hemodynamic correlates of left ventricular mechanical function in four groups of hearts. **Open symbols** refer to hearts receiving excess glucose and insulin supplements, **closed symbols** to hearts receiving no treatment; **bars** represent ± 1 standard error of the mean. **Upper panels** depict data, shown in squares, in control experiments in which coronary perfusion was maintained at normal flow rates; **lower panels** illustrate the changes noted with a critical restriction in total coronary flow, shown in **circles.** Left ventricular development of pressure was maintained during ischemia, but end-diastolic pressure increased progressively. LV = left ventricular.

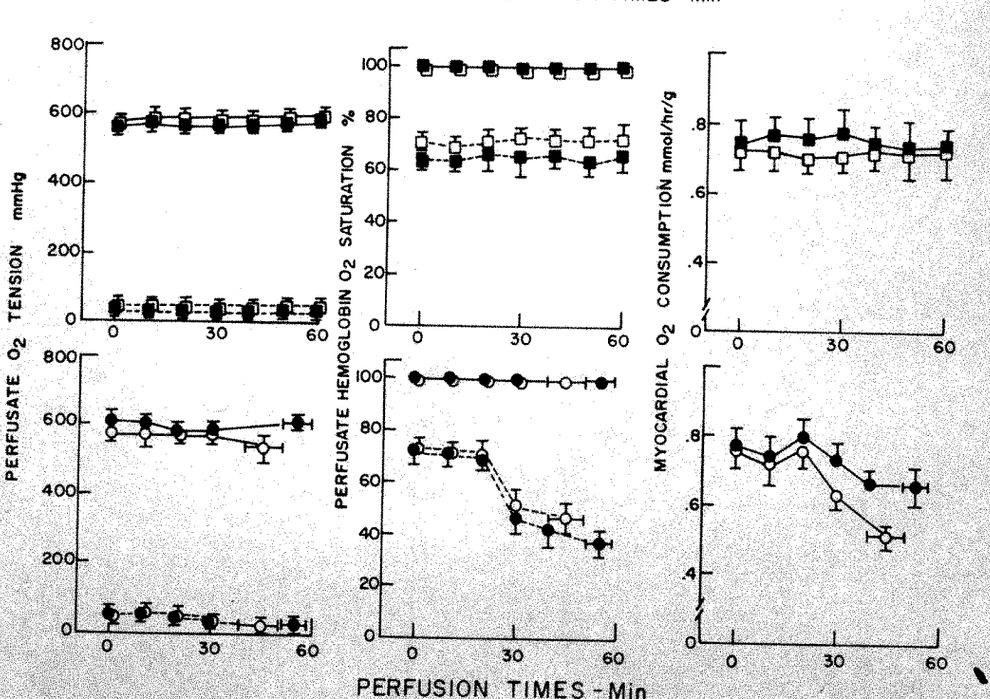

FIGURE 2. Values for perfusate oxygen tension, hemoglobin oxygen saturation and myocardial oxygen consumption in the same four groups of hearts. Hearts both with and without excess glucose and insulin supplements increased oxygen extraction from the perfusate (widened arteriovenous differences of oxygen tension and hemoglobin oxygen saturation) during ischemia **(lower panels)** but nonetheless underwent a reduction in myocardial oxygen consumption due to restricted oxygen availability. Symbols as in Figure 1. **Solid lines** connect arterial data points; **broken lines** connect venous data points.

slightly to maintain a constant level of left ventricular pressure development. Coronary flow (normalized for ventricular weight), pressure time per minute and left ventricular end-diastolic pressures were similarly comparable as a function of perfusion time in either group and between groups (Fig. 1).

At a common level of mechanical performance, control data for perfusate oxygen tension, hemoglobin oxygen saturation and calculated myocardial oxygen consumption in both nonischemic heart groups are shown in the upper panels of Figure 2. Extraction rates of oxygen, as reflected by the relatively constant arteriovenous differences for perfusate oxygen tension and hemoglobin oxygen saturation, were almost identical between groups, as were the calculated values for myocardial oxygen consumption (average 0.75 mmol/hr per g in hearts without glucose and insulin supplements; 0.72 mmol/hr per g in hearts with added glucose and insulin).

Fatty acid consumption and oxidation data are illustrated in Figure 3. Despite differences in glucose and insulin availability, free fatty acid uptake in both nonischemic heart groups varied linearly as a function of perfusate fatty acid concentrations (correlation coefficient r value for combined data = 0.95). Arterial concentrations of fatty acids in the closed loop coronary reperfusion system declined progressively during the 60 minute perfusion trial as fatty acids were taken up by the hearts, and the highest values of uptake in both groups occurred early in the experiment. Fatty acid oxidation, as estimated from the production of $^{14}CO_2$

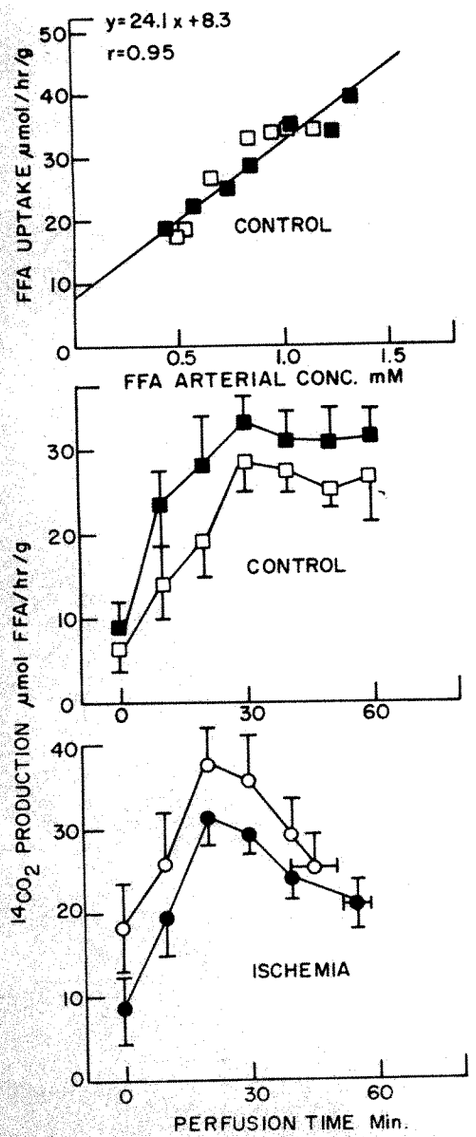

FIGURE 3. Free fatty acid (FFA) metabolic data in the same four groups of hearts. In control (aerobic) data, both with and without excess glucose and insulin, free fatty acid uptake related directly and linearly with free fatty acid arterial concentration **(upper panel).** Free fatty acid oxidation, as estimated from $^{14}CO_2$ production from labeled palmitate, required approximately 30 minutes to reach steady state levels **(middle panel)** with the coronary perfusion system as used in this preparation. During ischemia **(lower panel),** $^{14}CO_2$ production decreased by 34 and 35 percent, respectively, in hearts receiving either excess glucose and insulin supplements or no excess enrichment. CONC. = concentration.

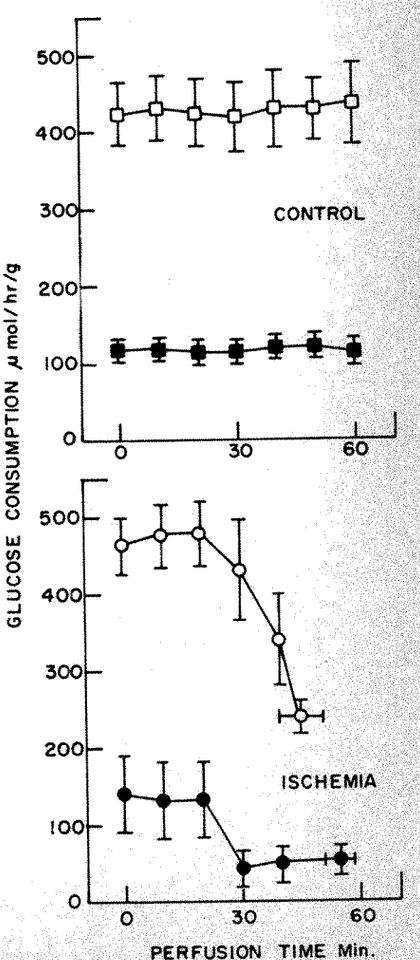

FIGURE 4. Glucose consumption data in the same four groups of hearts In control data **(upper panel),** the presence of high glucose and insulin levels caused a nearly fourfold increase in glucose uptake over levels of consumption in hearts receiving no excess substrate or hormone In both settings, the additional intervention of ischemia **(lower panel)** caused significant reductions in glucose uptake.

TABLE II

Tissue Concentrations of Glycolytic Metabolites (μmol/g)

	Glucose-6-P	Fructose-1,6-P	Triose*P	α Glycerol-P	Pyruvate	Lactate	Glycogen
Nonischemic hearts							
Without excess G/I	902.1 ±69.5	77.2 ±10.1	64.0 ±2.2	288.5 ±50.4	228.5 ±31.7	12.9 ±1.3	199.2 ±14.9
	NS	$P < 0.05$	$P < 0.005$	NS	$P < 0.05$	$P < 0.05$	$P < 0.05$
With excess G/I	956.0 ±99.0	48.5 ±8.5	44.8 ±4.8	427.1 ±81.2	379.3 ±76.4	22.4 ±3.0	238.6 ±13.8
	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.001$	$P < 0.05$	$P < 0.01$	NS
Ischemic hearts							
Without excess G/I	1224.7 ±86.3	121.2 ±10.8	104.7 ±17.7	2936.5 ±798.0	126.4 ±19.2	34.1 ±6.6	190.6 ±16.9
	$P < 0.01$	$P < 0.005$	$P < 0.01$	NS $P < 0.001$	NS $P < 0.05$	NS $P < 0.05$	NS
With excess G/I	876.0 ±62.6	198.2 ±23.9	133.8 ±23.4	2161.2 ±355.7	133.8 ±32.4	33.6 ±2.4	219.0 ±9.6

Data expressed as mean values ± 1 standard error of the mean.
* Triose includes both an estimation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate.
G/I = glucose and insulin; P = phosphate; *P* = probability.

from labeled palmitate, required approximately 30 minutes to achieve steady state values (mean value 31.5 μmol free fatty acid/hr per g in hearts without additional glucose and insulin, 28.5 μmol/hr per g in hearts with excess glucose and insulin). There were no statistical differences in values between groups at comparable time periods although availability and utilization of excess carbohydrate may have accounted for the slight decline in fatty acid oxidation.

Glucose metabolism was estimated both from glucose consumption, as determined from the coronary perfusate glucose levels (Fig. 4), and from glycolytic intermediates measured from frozen tissue samples of myocardium obtained from all hearts at the conclusion of each study (Table II). Significant differences in glucose metabolism were observed between the two control groups. Glucose consumption (Fig. 4) was enhanced nearly fourfold (428 versus 120 μmol/hr per g without glucose and insulin; $P < 0.001$, at comparable time periods). Tissue glycogen stores were greater ($P < 0.05$) in hearts supplemented with excess glucose and insulin; glycolysis also appeared greater (that is, intermediates of glycolysis [fructose-1,6-diphosphate and triose phosphates] were significantly less than in hearts without supplements) and products of glycolysis (α glycerol phosphate, pyruvate and lactate) were statistically or numerically greater.

Tissue concentrations of high energy phosphates and adenosine intermediates (Table III) were not different statistically in either nonischemic heart group, indicating a similarity in aerobic energy production, probably principally from fatty acid metabolism.

Ischemic hearts without excess glucose and insulin supplements: Total coronary flow was reduced in this group from 143 to 77 ml/min or 5.07 to 2.74 ml/min per g (46 percent reduction, $P < 0.001$). Ventricular fibrillation occurred in three animals before completion of the perfusion runs so that the group mean survival time was 55.2 ± 2.9 minutes or 25 minutes of total global ischemia (lower panels, Fig. 1). Heart rate and cardiac index were controlled throughout the course of perfusion to maintain an average peak aortic pressure of 94.9 mm Hg (Table I) and a pressure time per minute of 2,269 mm Hg sec/min (Fig. 1). Ischemia did effect a reduction in mechanical performance as reflected by the progressive increase in left ventricular end-diastolic pressure (7.5 mm Hg at 20 minutes versus 15 mm Hg at 55 minutes, $P < 0.05$) and a decrease in ventricular developed pressure (peak systolic-end diastolic pressure: 88 mm Hg at 20 minutes versus 78 mm Hg at 55 minutes, $P < 0.05$). Myocardial oxygen consumption decreased 18 percent (from 0.80 to 0.66 mmol/hr per g, $P < 0.01$) and was associated with widened arteriovenous differences of perfusate oxygen tension and oxygen hemoglobin saturation (Fig. 2).

Initial values for uptake of free fatty acid before ischemia were similar to values in control hearts as was time to equilibration of $^{14}CO_2$ production from labeled palmitate (Fig. 3). Between 20 and 55 minutes of perfusion, however, $^{14}CO_2$ production decreased 35 percent (31.8 to 21.0 μmol FFA/hr per g, $P < 0.025$) commen-

TABLE III

Tissue Concentrations of High Energy Phosphates and Adenosine Intermediates (μmol/g)

	Creatine Phosphate	Adenosine Triphosphate	Adenosine Diphosphate	Adenosine Monophosphate
Nonischemic hearts Without excess G/I	45.1 ±2.5	21.8 ±0.8	2.44 ±0.09	0.15 ±0.02
	NS	NS	NS	NS
With excess G/I	48.3 ±3.1	21.4 ±0.6	2.52 ±0.10	0.13 ±0.02
	$P < 0.001$	NS	$P < 0.001$	$P < 0.05$
Ischemic hearts Without excess G/I	21.1 ±4.0	19.2 ±2.1	3.52 ±0.12	0.23 ±0.04
	NS $P < 0.001$	NS NS	NS $P < 0.05$	NS $P < 0.05$
With excess G/I	24.6 ±3.7	20.1 ±0.5	3.28 ±0.32	0.23 ±0.04

Data expressed as mean values ± 1 standard error of the mean.

surate with the reduction in aerobic metabolism secondary to restrictions in total coronary flow.

Similar inhibitions were noted in glucose metabolism. Starting from preischemic glucose consumption values (Fig. 4) comparable with those of control hearts without excess glucose and insulin, ischemia resulted in a 56 percent reduction in glucose consumption (133 μmol/hr per g at 20 minutes versus 58 μmol/hr per g at 55 minutes, $P < 0.05$). Analysis of tissue concentrations of glycolytic metabolites (Table II) suggested an inhibition of intermediate metabolism between the triose phosphate and pyruvate steps, that is, lower values of pyruvate ($P < 0.05$ as compared with values in control hearts without glucose and insulin supplements), and higher values of glucose-6-phosphate ($P < 0.05$), fructose-1,6-diphosphate ($P < 0.05$), triose phosphates ($P < 0.05$) and α glycerol-phosphate ($P < 0.001$). The most likely location for this ischemic inhibition as suggested from anoxic rat heart data is at glyceraldehyde-3-phosphate dehydrogenase.[27] Ischemic changes in this group further included a slight reduction in tissue glycogen and significant increases in tissue lactate ($P < 0.01$) and adenosine mono- and diphosphates ($P < 0.05$ and < 0.001, respectively) (Table III), which were associated with a fall in creatine phosphate levels ($P < 0.001$).

Ischemic hearts with excess glucose and insulin supplements: Coronary flow was reduced from 167 to 85 ml/min or 5.31 to 2.70 ml/min/g (49 percent reduction, $P < 0.001$). Five hearts fibrillated prematurely after ischemia-induced mechanical failure, and mean survival time was only 45.4 ± 5.7 minutes, or 15 minutes of global ischemia (10 minutes less than in the ischemic hearts without glucose and insulin supplements). Mean hemodynamic data are shown in Table I and Figure 1. Despite adjustments in cardiac index, peak ventricular pressure and pressure time per minute could not be maintained terminally in response to progressive ischemia, and left ventricular end-diastolic pressure increased from 8.2 mm Hg at 20 minutes to 22 mm Hg at 45 minutes of perfusion ($P < 0.05$). The compromise in mechanical function was most apparent from the reduction in ventricular developed pressure (from 85 mm Hg at 20 minutes to 58 mm Hg at 45 minutes, $P < 0.005$), which was greater than that observed terminally in the ischemic hearts without glucose and insulin supplements ($P < 0.01$). The reduction in myocardial oxygen consumption was likewise greater (from 0.76 to 0.51 mmol/hr per g, −33 percent, $P < 0.005$) (Fig. 2), probably reflecting both the reduction in oxygen supply and the decreased oxygen need from reduced mechanical performance.

Initial values for free fatty acid uptake in this group before ischemia were similar to the initial data in the ischemic group without supplements and to the levels in both groups of nonischemic hearts. Fatty acid oxidation was somewhat greater than in the ischemic group without supplements (not statistically different at 30 minutes) but decreased thereafter to approximately the same extent (−34 percent, from 38.5 to 25.6 μmol FFA/hr per g, $P < 0.05$) (Fig. 3).

Glucose consumption data before coronary flow restriction were similar to those in nonischemic hearts with excess glucose and insulin (Fig. 4) and were almost fourfold greater than in hearts without excess glucose and insulin. As in the untreated ischemic hearts, decreases in coronary flow caused a progressive inhibition in glucose consumption (from 483 μmol/hr per g at 20 minutes to 242 μmol/hr per g, $P < 0.005$). A buildup in glycolytic intermediates before glyceraldehyde-3-phosphate dehydrogenase was again noted ($P < 0.001$ for fructose-1,6-diphosphate as compared with findings in nonischemic hearts with supplements, and $P < 0.01$ for trioses) along with a reduction ($P < 0.05$) in tissue pyruvate. Lactate was increased ($P < 0.05$) and glycogen was slightly reduced. As compared with values in ischemic hearts without supplements, glucose transport appeared greater (glucose-6-phosphate less, $P < 0.01$),

but accumulation of fructose-1,6-diphosphate was also increased ($P < 0.005$).

Ischemia imposed significant reductions in creatine phosphate ($P < 0.001$) and significant elevations of adenosine mono- and diphosphates ($P < 0.05$ and $P < 0.05$, respectively) over values in nonischemic hearts with supplements (Table III). There were no differences in high energy phosphates or adenosine intermediates from ischemic hearts without additional glucose and insulin.

Thus, increased availability of glucose and insulin in aerobic hearts promoted increased glycogenesis and glycolysis but did not further increase energy production over that of hearts with no added substrate and hormone. Global ischemia, even though mild to moderate in amount, caused mechanical failure and electrical instability that were correlated metabolically with inhibitions of glucose consumption, fatty acid oxidation, depletions of high energy phosphates and buildup of intermediate metabolites. In this setting, high levels of glucose and insulin appeared to compromise further mechanical and electrical functions and did not cause an efficacious increase in either glycolytic flux or energy production as estimated from tissue stores of glycolytic intermediates and high energy phosphates.

Discussion

The proposed efficacy of glucose-potassium-insulin infusions in the treatment of patients with acute and chronic ischemic heart disease[1–5] was based on an array of theoretical speculations including (1) potential enhancement of energy production through anaerobic glycolysis,[28] (2) repletion of intracellular potassium deficits lost during myocardial ischemia, (3) possible antiarrhythmic properties,[3,29,30] and (4) restoration of depleted insulin reserves that result from cardiac dysfunction.[31] Unfortunately, the early reports of success have not been confirmed in any large clinical series, and both the results and theoretical bases of the treatment have been challenged.[6–10,32,33] These contradictions obviously require explanation before glucose-potassium-insulin solutions can be recommended for further clinical use, and it is hoped that laboratory and clinical investigations now in progress may help to define the mechanisms that operate therapeutically.

Animal studies to date have not produced agreement on the mechanisms of metabolic action that derive from glucose-potassium-insulin therapy, but certain data suggest that potassium has only a minor influence and that the major effects are due to glucose and insulin.[11,12] The relative influence of these two agents on glucose metabolism and accelerated anaerobic glycolysis remains controversial, possibly, as Rovetto et al.[13] have pointed out, because the type of anaerobic stress applied to mammalian heart muscle has not been standardized. Their data indicate that anoxia (oxygen deprivation through reductions in coronary perfusate oxygen tension at normal or high coronary flow levels), as employed in several early studies, and ischemia (oxygen deprivation through reductions in coronary flow at normal or high perfusate oxygen tension levels) have diametrically opposite effects on carbohydrate utilization. Maroko et al.[11] and Opie et al.,[12] using coronary ligation techniques (ischemia) in intact dogs and baboons, demonstrated a beneficial effect with systemically administered glucose and insulin as evidenced by increased intracellular deposits of glycogen, greater tissue stores of high energy phosphates or less morphologic cell injury in ischemic myocardium. Reasons for these findings were unclear, but Opie et al. were unable to show increased glycolysis in the ischemic/infarcted zones, although improved glycolysis was suggested in the nonischemic zones.

Global versus regional myocardial ischemia model: The presence of accelerated glycolysis could not be identified in the ischemic hearts with glucose and insulin supplements in our study using a blood-perfused controlled coronary circulation technique in a large mammalian working swine heart preparation. Possible differences between this preparation and the previously mentioned models of regional coronary occlusion include species differences, use of a global form of myocardial ischemia rather than a regional pattern of underperfusion, use of an isolated circuitry for control of the coronary perfusion in which total coronary flow was critically reduced but not taken to zero flow level in any particular arterial circulation, control of substrate and hormone levels in the coronary perfusate and direct application of the substrate and hormone treatment to the ischemic myocardium.

The swine heart, unlike that of the rat and dog, closely resembles the heart of man and other primates in cardiovascular function, size and anatomy and perfusion distributions and collateral flow of the coronary arteries.[34–39] It thus appears useful as an experimental analog to man. The global form of ischemia was chosen to maximize the homogeneity of myocardial ischemia (although ischemic gradients from endocardium to epicardium were no doubt present) and to improve the quantitative estimates of metabolic performance. We recognize that this global pattern of underperfusion is not strictly analogous to that in clinical atherosclerosis, except in cases of severe multivessel coronary artery disease. However, experimental studies using coronary occlusive techniques have demonstrated that in regional ischemia a variety of coronary flow patterns and populations of normal and ischemic cells exist in the area of tissue supplied by the occluded artery. Because of this heterogeneous distribution of normal, ischemic and irreversibly damaged cells, it is impossible to sample and measure accurately only those metabolic changes occurring in ischemic tissue and to correlate them with reductions in coronary flow. To circumvent these problems of admixture, a global pattern of oxygen deprivation was developed. The control of levels of substrate media in the coronary perfusate was designed to aid in accurately monitoring substrate consumption levels in normal and ischemic myocardium and to eliminate extraneous contamination of catecholamines and other cardioactive agents from the periphery. Even in the absence of red blood cells, which were provided in this study, these media have been used extensively

in the past as an experimental coronary perfusate[13,15,19] without untoward effects and, as such, should not have artifactually distorted findings in this study.

Effects of glucose and insulin supplements on mechanical and metabolic cardiac functions: Our data showed no obvious benefits of glucose and insulin supplements on either mechanical or metabolic functions. If anything, at the mild to moderate constraints in coronary blood flow imposed on the two ischemic groups, decreases in mechanical performance, that is, increases in left ventricular end-diastolic pressure and decreases in ventricular developed pressure, were more pronounced in hearts receiving excess substrate and hormone. Similarly, mean survival time was 10 minutes less in the treated group. The availability of excess glucose and insulin in no way altered the significant inhibitions in either glucose consumption or free fatty acid oxidation that occurred in response to restrictions in coronary flows. As reported from isolated anoxic rat hearts,[27] our swine heart data identified a presumably identical location for obstruction in ischemic glycolytic flux, at glyceraldehyde-3-phosphate dehydrogenase, an enzyme acutely sensitive to anoxic and ischemic events including intracellular buildup of lactate, nicotine adenine dinucleotide (reduced form) and hydrogen ion. Myocardial exposure to increased circulating levels of glucose and insulin did not surmount this obstruction in glycolytic metabolism and may in fact have accounted for increased buildup of certain intermediate metabolites (fructose-1,6-diphosphate).

Effects on energy production: Estimates of energy (ATP) production from aerobic and anaerobic glycolysis were also determined from our data. Previous studies have shown that in aerobic hearts rates of glucose utilization are dependent on the availability and concentration of glucose and insulin in the blood.[40–42] Our data indicate that this same relation holds true in aerobic hearts with and without glucose and insulin supplements. Unfortunately, the contribution of ATP production from glycolysis in anaerobic hearts appeared insufficient to counterbalance favorably the debt incurred from reductions in oxygen metabolism.

If total ATP production is calculated from glycolysis using 2ATP for each glucose traversing the Embden-Meyerhof pathway and from oxygen consumption using a P/O ratio of 3:1, contributions of energy production from glycolysis and oxidative metabolism can be estimated in the two ischemic groups with and without excess glucose and insulin. For the purposes of calculation, it was assumed that the glucose consumption data in each group reflected quantitatively the rate of glycolytic flux. In ischemic hearts receiving no supplements, the percent of total ATP production from glycolysis and oxidative sources was, respectively, 6 and 94 percent in the control (preischemic) period and 3 and 97 percent at the terminal point of ischemia; these values were similar to previous results.[43] In the ischemic group receiving excess glucose and insulin, the contribution of glycolysis to total ATP production (5,394 μmol ATP/hr per g) in the control period was increased to 18 percent. However, after the induction of global ischemia in this group, total ATP production at 45 minutes of perfusion decreased (to 3,544 μmol ATP/hr per g) as did the percent derived from glycolysis (13.6 percent). Thus, glycolysis as an energy source was incapable of compensating for the ATP lost through reductions in oxidative metabolism, despite the presence of high glucose and insulin levels. Furthermore, the loss of glycolytically produced ATP may also promote instability of cell transmembrane electrical activity,[44] which may in part account for the increased incidence of ischemic dysrhythmias.

Possible explanation for reported benefits of glucose-insulin-potassium therapy: Given the present evidence that glucose and insulin are incapable of augmenting energy production through accelerated glycolysis in the ischemic myocardium, what alternative explanations exist for the reported benefits of glucose-insulin-potassium therapy? Brachfeld[10] has suggested some possibilities including the multivalent actions of insulin on cell metabolism and contractility, the importance of potassium in correcting systemic hypokalemia if present, and the possible salutary effects of glucose-insulin-potassium action as a hyperosmolar solution on the ischemic myocardium. Trials using both dextran and mannitol as blood volume expanders in clinical and animal studies have shown improvement in mechanical function, coronary blood flow and anginal threshold after increases in serum osmolarity.[45,46] However, the volumes and concentrations of the hyperosmolar agents required to effect these improvements are necessarily large and Lesch et al.,[9] using glucose infusions sufficient to elevate the blood glucose concentration to 300 to 500 mg/100 ml, saw no improvement subjectively or in terms of hemodynamic or electrocardiographic changes in patients with coronary artery disease undergoing cardiac catheterization. In our study, the moderate increases in serum osmolarity,[47] as expected from blood glucose concentrations of 26.6 mM (478 mg/100 ml) in the coronary perfusate of hearts with glucose and insulin supplements, similarly effected no improvement in either metabolic or mechanical variables during mild to moderate ischemia.

To these suggestions may be added recent evidence indicating that insulin as such is essential not only for proper glucose metabolism, but also for adequate intramyocardial protein synthesis and for prevention of lysosomal activation and release of hydrolytic enzymes into the cytosol.[48–50] Such antiinflammatory properties may be advantageous in protecting jeopardized tissue during ischemic insult. Finally, benefits from glucose-insulin-potassium infusion have been reported only in clinical and laboratory studies in which the solution was administered systemically (as recommended by Sodi-Pallares) rather than infused selectively into the coronary perfusate. One interpretation of this observation is a possible primary effect of the solution or its components at a site other than the heart, which may then secondarily improve or protect cardiac muscle during ischemia. Such an effect may be the action of glucose-insulin-potassium, or specifically insulin, on the circulating blood levels of free fatty acid. It is known that

fatty acids, both at physiologic and greater concentrations, can increase the incidence of serious ventricular arrhythmias in ischemic myocardium,[51,52] and in the isolated rat heart may even promote the development of myocardial infarction.[53] Glucose-insulin-potassium and insulin decrease substantially the circulating free fatty acid concentrations,[12,53] probably by the inhibitory influence of insulin on lipolysis in adipose tissue,[54–56] and this effect could explain the reported efficacy of glucose-insulin-potassium solutions.

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Failure of Hyaluronidase to Alter the Early Course of Acute Myocardial Infarction in Pigs

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The effect of hyaluronidase on the early course of acute myocardial infarction was evaluated in closed chest anesthetized pigs. One hour after balloon catheter occlusion of the left anterior descending coronary artery, hyaluronidase (500 units/kg body weight) was rapidly infused in 10 animals while 9 received no treatment. The animals were then observed over the next 4 hours. Cardiac output, heart rate, mean arterial pressure and left atrial pressure were not significantly affected by treatment. Heart rate increased and arterial pressure decreased in each group to a comparable degree by 5 hours, but left atrial pressure and cardiac output were unaffected.

Precordial S-T segment mapping revealed no significant difference between the two groups. S-T segments rose to a comparable degree in each group and peaked before 1 hour. Hyaluronidase had no acute effects on the S-T segment map in the first 30 minutes after infusion or during the subsequent return of the map toward control level. Slightly lower S-T segments in the hyaluronidase-treated group at 5 hours was of borderline significance but was attributed to factors other than the drug intervention. Changes in ventricular wall motion were assessed angiographically, and all animals manifested akinetic or dyskinetic segments. A significant reduction in shortening fraction of involved segments was seen after occlusion, but no difference was observed between the two groups at 5 hours. Shortening fraction of the combined anterior and anteroapical segments decreased from 66 ± 10 to 20 ± 6 percent at 5 hours in the hyaluronidase group (no. = 7) whereas in the control group (no. = 6) it decreased from 68 ± 6 to 28 ± 9 percent. Comparable increases in end-diastolic volume were also present at 5 hours in each group. Volumes increased from 80.6 ± 5.1 to 97.5 ± 6.4 ml^3 at 5 hours ($P < 0.05$) in the hyaluronidase-treated group (no. = 10) compared with 86.9 ± 8.9 to 104.8 ± 11.0 ml^3 ($P < 0.05$) in the control group (no. = 8).

Hyaluronidase did not alter the early course of acute myocardial infarction in pigs. Species differences may contribute to different results reported to date.

Hyaluronidase, an enzyme that depolymerizes and hydrolyzes hyaluronic acid, is undergoing clinical evaluation as an agent to minimize myocardial infarct size.[1] Although a report describing this application in man was published as early as 1959,[2] with subsequent studies reported as recently as 1965,[3] hyaluronidase subsequently received little attention until recent animal studies[4,5] renewed interest. Although the precise mechanism of action is not established, the depolymerization of hyaluronic acid is thought to facilitate the diffusion of substrates through the interstitial space. In areas where blood supply is marginal after acute coronary occlusion, augmented diffusion of substrates into, and metabolic products out of, the ischemic area could have significant impact on tissue survival.

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Maroko et al. have shown hyaluronidase to limit infarct size in dogs 24 hours after acute coronary occlusion[4] and to improve the ability of a perfused dog heart to tolerate reduced rates of coronary blood flow.[5] However, a clinical evaluation[1] is necessarily limited in the type of invasive studies that can be employed. This investigation was undertaken to study the effect of hyaluronidase on acute infarction in the closed chest pig, combing precordial S-T segment mapping, hemodynamic measurements and an angiographic assessment of ventricular wall motion. The pig was chosen as the experimental model since its coronary circulation closely resembles man's, suggesting that it may be a more appropriate model than the dog for studying experimental therapy.[6,7]

Material and Methods

Farm-bred pigs (45 to 65 kg) were anesthetized with sodium pentobarbital, 35 mg/kg bodyweight and chloralose, 60 mg/kg intravenously, and placed supine. The animals were tracheotomized but allowed to maintain spontaneous respirations. Oxygen was administered through the tracheotomy, if necessary, to maintain arterial partial oxygen tension between 80 and 105 mm Hg. For subsequent anesthesia, chloralose was the primary agent with infrequent reliance on additional small doses of sodium pentobarbital. All animals were anticoagulated with heparin, 0.3 mg/kg intravenously, at the beginning of the procedure, and half this dose was given again 4 hours later.

Instrumentation

An 18 lead precordial electrocardiographic map was sewn subcutaneously on the chest and wire electrodes were connected to a junction box to permit simultaneous recording of three electrocardiographic leads. The animal was then rotated into the 30 ° right anterior oblique position for the remainder of the study. A thermistor catheter was placed in the pulmonary artery for obtaining cardiac output by thermodilution technique (Columbus Instruments, Columbus, Ohio) and a short arterial catheter connected to a Statham 23Db transducer was placed in the femoral artery for monitoring arterial blood pressure. A no. 8F Eppendorf catheter was passed retrograde to the left atrium from a femoral arterial cutdown site. This catheter was connected to a Statham 23Db transducer to monitor mean left atrial pressure and also to serve as the route for injecting contrast material for angiography. The zero reference level for pressure measurement was one third of the distance from the table top to that superior portion of the chest wall aligned with the mid-heart with the animal in the right anterior oblique position.

For left ventriculography 15 ml of sodium and meglumine diatrizoates (Hypaque-M 75 percent®) was injected at 150 to 250 lb/in^2 (10–17 × 10^5 pascals) into the left atrium. Ventriculograms were recorded at 60 frames/sec on Kodak XX film using a 6 inch (15 cm) image intensifier and a 75 mm lens. The same fixed distance from X-ray tube to image tube was used during all studies, and a calibration grid was filmed at mid-chest level for subsequent use in left ventricular volume determination. The latter determination was carried out with a Hewlett-Packard 5693A left ventricular volume analysis subsystem using the area-length method for single plane ventriculograms described by Sandler and Dodge.[8]

Coronary occlusion was accomplished as previously described.[9] Under fluoroscopic guidance, a shortened no. 8F thin-walled Cournand catheter was passed through a right carotid arteriotomy into the proximal left anterior descending coronary artery. A no. 3F Fogarty embolectomy catheter (Edwards Laboratory) was next passed through the larger catheter and its tip positioned in the approximate midleft anterior descending coronary artery. The larger catheter was then withdrawn into the aorta and the embolectomy catheter balloon "inflated" with mercury to occlude the coronary vessel. A closed stopcock then sealed the balloon catheter, preventing balloon collapse.

Protocol

The precordial electrocardiographic map (paper speed 25 mm/sec, 1 mv = 20 mm) was recorded simultaneously with left atrial and arterial blood pressure after cardiac output measurement by thermodilution technique (using 10 ml of saline solution at room temperature per determination and requiring agreement of closer than 10 percent between consecutive measurements). A left ventriculogram was next performed, completing the control studies. The coronary vessel was then occluded. With the exception of the ventriculogram these measurements were repeated thereafter at 1, 1 1/2, 2, 3, 4 and 5 hours after occlusion. Ventriculography was carried out before occlusion and 1, 1 1/2, 3 and 5 hours after occlusion. Hyaluronidase (Alidase®, Searle) was infused over 5 minutes (500 U/kg) immediately after the collection of data 1 hour after occlusion. Arterial blood gases were monitored frequently to assure adequate oxygenation. Lidocaine was routinely given 5 minutes after occlusion (100 mg bolus injection intravenously followed by a drip infusion, 2 mg/min, for the duration of the study). Direct current defibrillation and further bolus injections of lidocaine were used as clinically indicated. At the conclusion of the study, the animals were killed.

Ten animals were treated with hyaluronidase and nine served as untreated control animals.

Data Analysis

S-T segment map: S-T segment elevation was measured 100 msec after the onset of the QRS complex. Any leads having a negative S-T segment at any time during the study were eliminated from analysis; this was an infrequent occurrence. The 18 lead values were averaged at each mapping period, and the resultant mean S-T elevation ($\overline{ST}$) was used throughout this analysis.

Angiographic analysis of wall motion: End-diastolic and end-systolic frames were identified by careful frame by frame analysis of cine films and were traced on clear acetate sheets for subsequent analysis. Premature beats were rare with left atrial injections but, when present, the immediate postpremature beat was excluded from analysis. End-diastolic volumes were determined as described earlier. Ventricular wall motion was analyzed by drawing a longitudinal axis from the apex to the aortic-mitral valve junction. This longitudinal axis was trisected, resulting in eight left ventricular sectors. The end-systolic (ES) and end-diastolic (ED) areas of each sector were determined by planimetry and a "shortening fraction" (percent) determined for each sector using the equation: SF = (ED-ES/ED) × 100. The sector most depressed at 1 hour of occlusion (that sector whose shortening fraction at 1 hour showed the greatest absolute decrease from control data) was identified, and its changes in shortening fraction were analyzed. In addition, the anteroapical segment and the anterior segment immediately superior to this segment were analyzed separately and in combination. These sectors were chosen

since they lay in the area presumably most dependent on perfusion by the occluded vessel.

Statistics: Data were analyzed by Student's t test for groups and by paired t test where changes within groups were examined. A P value of <0.05 was considered the lower level of significance.

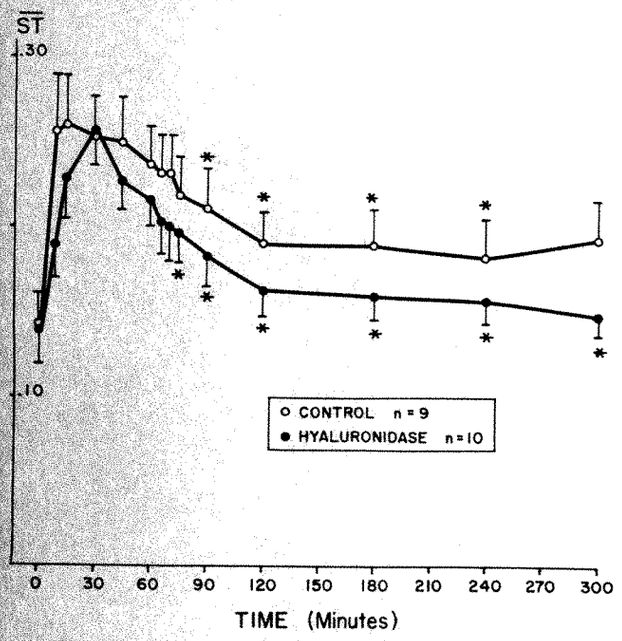

FIGURE 1. Mean S-T segment elevation ($\overline{ST}$) in millivolts after coronary occlusion in pigs receiving either hyaluronidase (no. = 10) or no treatment (no. = 9) at 1 hour of occlusion. Data are expressed as mean values ± standard error of the mean. No significant difference is noted between the two groups at any time ($P > 0.05$). * = differs significantly from the 1 hour value.

Results

Hemodynamics (Table I)

Heart rate was slightly higher in the control group at 1 and 2 hours of occlusion but at 3 to 5 hours it was similar in the two groups. Cardiac output similarly was somewhat higher at 1 1/2 and 2 hours in the control animals but at 3 to 5 hours was not significantly different. Arterial and left atrial pressures did not differ between the two groups at any time during the study. When the 1 hour and 5 hour values are contrasted within each group, arterial pressure decreased significantly in both groups ($P < 0.01$) whereas cardiac output and left atrial pressure did not differ.

S-T Segment Map

Mean S-T elevation ($\overline{ST}$) for the two groups is shown in Figure 1. Similar peak $\overline{ST}$ values were observed in the two groups and the reduction in $\overline{ST}$ between 1 and 1 1/2 hours was significant in both groups. The difference at the 5th hour was of borderline significance ($T = 2.1076$, $P \sim 0.05$) with $\overline{ST}$ being lower in the treated group. The widened difference was partly due to an increase in $\overline{ST}$ in the control group at 5 hours of occlusion. In addition, $\overline{ST}$ in the treated group was already lower than control level at 1 hour (before treatment) although this difference was not significant. When $\overline{ST}$ was expressed as either percent of peak $\overline{ST}$ or percent of the 1 hour $\overline{ST}$ value, no significant differences emerged between the two groups (Fig. 2).

Although 10 animals required direct current countershock after coronary occlusion, this intervention had no significant effect on the $\overline{ST}$ segment map. Eight of the 10 episodes requiring countershock took place within the first 30 minutes of occlusion and were equally distributed between the two treatment groups. The two

TABLE I

Hemodynamic Data Before and After Coronary Occlusion in 10 Pigs Receiving Hyaluronidase (H) and 9 Receiving No Treatment (C) at 1 Hour of Occlusion (mean ± standard error of the mean)

		Hours of Occlusion					
	Control	1	1 1/2	2	3	4	5
Cardiac output (liters/min)							
H	6.3 ± 0.6	5.0 ± 0.5	4.3 ± 0.4(9)	4.5 ± 0.3	5.0 ± 0.4	5.0 ± 0.4	4.9 ± 0.4
C	6.2 ± 0.5	6.5 ± 0.6(8)	5.9 ± 0.5*	5.9 ± 0.5†	5.9 ± 0.6	6.4 ± 0.6	5.8 ± 0.6
Heart rate (beats/min)							
H	150 ± 13	150 ± 10	151 ± 9	148 ± 8	175 ± 8	174 ± 9	175 ± 7
C	163 ± 11	186 ± 10*	182 ± 13	181 ± 10*	180 ± 12	185 ± 11	184 ± 9
Mean arterial blood pressure (mm Hg)							
H	136 ± 8	141 ± 6	142 ± 6	144 ± 7	140 ± 8	132 ± 6	117 ± 6
C	146 ± 6	139 ± 5	138 ± 5	136 ± 5	128 ± 4	122 ± 5	115 ± 5
Mean left atrial pressure							
H (9)	6.3 ± 1.3	6.3 ± 0.9	5.8 ± 1.0	7.2 ± 1.7	7.6 ± 1.9	7.4 ± 2.0	6.0 ± 1.3
C	6.7 ± 1.7	7.4 ± 1.7	8.2 ± 1.8	8.3 ± 1.7	7.6 ± 1.6	6.8 ± 1.3	6.4 ± 1.5

*$P < 0.025$; †$P < 0.05$ (significance of difference between C and H groups). Figures in parentheses indicate number of animals.

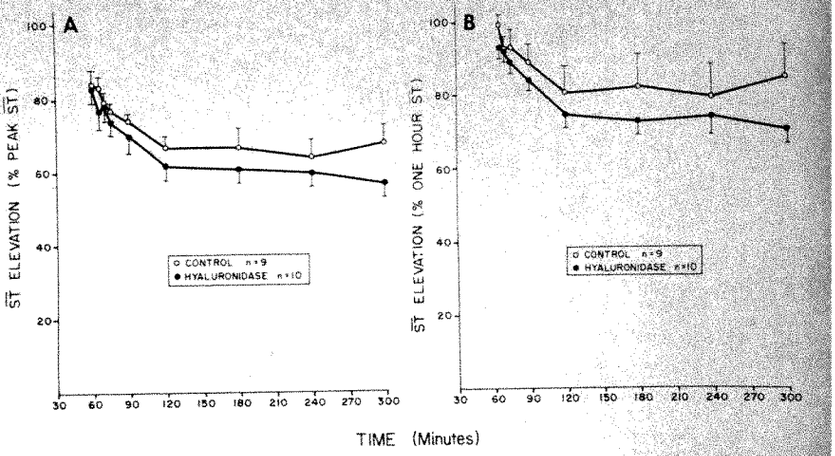

FIGURE 2. Mean S-T segment elevation ($\overline{ST}$) one to five hours after coronary occlusion in pigs receiving either hyaluronidase or no treatment at 1 hour of occlusion. **A,** expressed as a percent of the peak $\overline{ST}$ value (mean ± standard error of the mean). **B,** expressed as a percent of the 1 hour $\overline{ST}$ value. No significant difference is present between the two groups at any time ($P > 0.05$).

remaining episodes involved the hyaluronidase-treated group, one at 2 hours and the other at 3 hours of occlusion.

Ventriculographic Analysis

Volumes: Preocclusion end-diastolic volumes were similar in the control (86.9 ± 8.9 ml^3, no. = 8) and hyaluronidase-treated animals (80.6 ± 5.1 ml^3, no. = 10). Volumes increased significantly in each group ($P < 0.01$) by 1 1/2 hours of occlusion and remained significantly increased thereafter when compared with preocclusion values. At 5 hours the final volumes were 104.8 ± 11.0 ml^3 in the control group and 97.5 ± 6.4 ml^3 in the group that received hyaluronidase. At no point did the volumes differ significantly between the two groups and in neither group did the 5 hour value differ significantly from that at 1 hour.

Sector wall motion analysis: Analysis of sector wall motion in either the most involved area (Fig. 3), anteroapical, anterior or combined anterior-anteroapical areas revealed no significant difference between the two groups. Control sector shortening fractions were similar in each anatomic subset, and the degree of depression was also similar in all groups. When data from the anterior and anteroapical areas are combined, sector shortening fractions decreased from 66 ± 10 percent before occlusion to 20 ± 6 percent at 5 hours of occlusion ($P < 0.05$) in the hyaluronidase-treated group (no. = 7) and from 68 ± 6 to 28 ± 9 percent in the control group ($P < 0.05$).

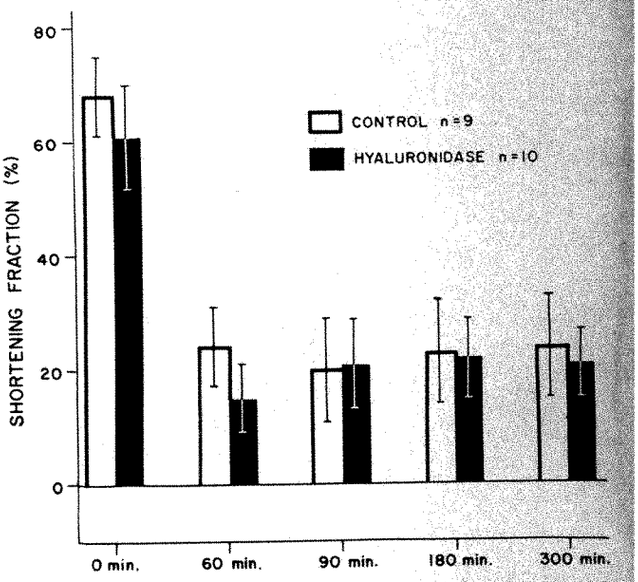

FIGURE 3. Shortening fraction (percent) of the most depressed segment of the left ventricle before (0 min.) and after coronary occlusion in pigs receiving either hyaluronidase or no treatment at 1 hour of occlusion. **Bars** represent mean values ± standard error of the mean. No significant differences were noted between the two groups at any time during the study.

Discussion

The use of hyaluronidase to treat acute myocardial infarction in man is currently under investigation. Interest in this intervention was first reported in 1959, when a summary paper[2] described studies in dogs and patients in which hyaluronidase was given during the acute phase of myocardial infarction. The enzyme seemingly had a beneficial effect on a variety of electrocardiographic abnormalities that developed as a result of the acute infarction process, but that study was uncontrolled and involved no randomization with other treatment schedules. The proposed mechanism of action was related to a reduction in tissue edema in the damaged area, diminishing fiber injury and facilitating collateral circulation. This general concept is of considerable interest today, although not specifically in connection with hyaluronidase therapy.[10]

Maroko et al.[4] reported hyaluronidase to diminish myocardial necrosis in dogs after coronary occlusion primarily on the basis of finding smaller than expected reductions in myocardial creatine phosphokinase (CPK) in areas of myocardium showing current of injury 24

hours earlier. Fewer histologic changes and less glycogen depletion paralleled the CPK preservation. In their study, hyaluronidase was infused 30 minutes after occlusion. In addition, brief 20 minute occlusions in two animals resulted in less S-T elevation when hyaluronidase preceded the second period of occlusion. The immediate (15 minute) effect of hyaluronidase on S-T elevation was a significant reduction when compared with findings in control animals in which no significant reduction occurred. No significant hemodynamic change was attributed to hyaluronidase although the hemodynamic details of these experiments were not presented. A subsequent study using a partially perfused dog heart[5] showed that pretreatment with hyaluronidase provided greater tolerance for restriction of coronary flow, as judged by elevation of left atrial pressure. In these studies a 49 percent reduction in left coronary arterial blood flow resulted in a significant increase in left atrial pressure (from 3.5 to more than 20 mm Hg).

In man a recent preliminary report[1] has shown that S-T segment elevation during the early acute phase of myocardial infarction is lowered significantly as early as 2 and as late as 24 hours after administration of hyaluronidase.

In our investigation three aspects of acute myocardial infarction were studied: (1) hemodynamics, (2) S-T segment changes, and (3) left ventricular wall motion abnormalities. The extent of infarction was sufficient in each case to produce readily observable akinetic and occasionally dyskinetic wall motion abnormalities in the ventriculogram. Marked S-T segment elevation was also noted and in a few cases transient intraventricular conduction defects were noted, implying septal ischemia and possibly more proximal occlusion.

Hemodynamics: Hemodynamic data revealed no major differences in the treated and untreated animals. Failure of left atrial pressure to increase in the early stage of infarction at a time when end-diastolic volume was increasing is consistent with the initial increase in compliance described by Forrester et al.[11] Since significant hemodynamic compromise did not result from this degree of infarction, there was little room for improvement due to any therapeutic modality. A slight variation in the time course of hemodynamic changes was noted, but by 5 hours of infarction the two groups were indistinguishable.

Precordial S-T mapping: Previous studies in our laboratory have used the precordial electrocardiographic map to assess the extent of myocardial injury. Coronary reperfusion 1 hour after occlusion resulted in an abrupt decrease in S-T segment elevation,[12] and withdrawal of the occluder to a more proximal position resulted in heightened S-T segments.[9] These studies and those of others[13,14] provide a basis for using this technique to assess the effect of interventions such as administration of hyaluronidase.

Mean S-T segment elevation ($\overline{ST}$) similarly showed only minimal differences between the groups. A difference of marginal significance was observed at 5 hours as the result of a slight rise in $\overline{ST}$ in the control group and a slight decrease in the treatment group. When $\overline{ST}$ was expressed as a percent of the 1 hour value or as percent of the peak $\overline{ST}$ value, no significant differences were seen. It would appear that hyaluronidase had no significant effect on the S-T segment elevations in the acute phase of infarction.

The timing of the intervention in this and previous reports differ. In the experiments reported by Maroko et al.,[4] hyaluronidase was given 30 minutes after occlusion, a time when the dogs' S-T segment abnormality was at a plateau. In our study, hyaluronidase was given to the pigs at 1 hour of occlusion, a time when a significant decline in mean S-T segment elevation ($\overline{ST}$) was taking place. The decline in $\overline{ST}$ between 1 and 1 1/2 hours of occlusion was significant in both the hyaluronidase-treated and control group and comparable in degree.

In the series of dogs reported in 1972, Maroko et al.[4] administered hyaluronidase as a bolus injection in a dose of 225 units/kg 30 minutes after occlusion and observed changes at 24 hours. One small subgroup received 500 units/kg and no hemodynamic effect was observed. In a recent clinical report,[1] hyaluronidase was administered in a dose of 500 units/kg with additional clinical doses at 2 and 6 hours and every 6 hours thereafter until 42 hours elapsed since the initial dose. Significant lowering of S-T segments attributed to the drug was noted as early as 2 hours but was present at 6 hours as well. In our investigation, a single bolus injection of hyaluronidase was administered in the same dose employed in the clinical trial. Failure to observe S-T segment changes comparable with those reported would not appear to be a dose-related phenomenon.

Ventricular wall motion: Mechanical function of the myocardium is a variable of great importance since it reflects viability in the most meaningful sense. Failure to observe improvement in ventricular wall motion after the administration of hyaluronidase is consistent with the failure to observe a significant alteration in the S-T segment abnormalities. Recent work in our laboratory[12] has shown that the S-T segment elevation may "improve" coincident with persistent mechanical dysfunction and the development of extensive intramural hemorrhage.

Explanation for different responses of dog and pig infarcts: Preliminary studies in our laboratory on coronary blood flow in the pig (using 7 to 10 μ radioactive-labeled microspheres) after acute coronary occlusion indicate that the central infarct zone is essentially devoid of blood flow. The dog, on the other hand, has a significant inflow into the infarct zone,[15,16] suggesting that in the dog infarcts are only partially ischemic and that pharmacologic agents may have more ready access to the ischemic area. The situation in man is less well explored but in all likelihood is more variable owing to the variable contribution of collateral vessels from case to case. With such severe core ischemia, it seems reasonable to expect that the infarct in the pig would be less amenable to modification by pharmacologic interven-

tions. In addition, recent work[16] suggests that myocardial blood flow in the infarct zone of the dog increases progressively for 2 hours after occlusion, whereas a similar potential has not been reported in the pig heart. These differences (that is, the more absolute ischemia in the pig infarct zone and the apparent progressive increase in core infarct perfusion in the dog) could contribute to the different response to hyaluronidase observed in the two animals.

Although no significant beneficial effects were noted immediately after administration of hyaluronidase in our study, we recognize that hemodynamic recovery after myocardial infarction is a process that takes place over a period of weeks.[17] Benefits may be observed well beyond the very immediate period of study reported here, and have indeed recently been reported to take place in dogs after reperfusion of acutely ischemic myocardium.[18]

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Simple Method for Computer-Aided Analysis of Echocardiograms

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The use of echocardiography in the diagnosis and assessment of heart disease is increasing as greater familiarity is obtained with this noninvasive procedure. Quantitative evaluation of echocardiographic studies has heretofore required time-consuming manipulation of mathematical formulas. A simple method utilizing a sonic digitizing tablet has been developed for computer-aided analysis of M-mode echocardiograms. This device can convert a point located manually with a digitizing pen into X and Y coordinates and with use of the standard telephone network can communicate on a time-shared basis with a DECSYSTEM-10 computer.

A program has been written to compute and type the results of standard calculations involving mitral valve motion and left ventricular function. The information can also be stored on disk by the computer for future use. This simple, relatively inexpensive system is valuable because of the ease with which it permits usually laboriously obtained information to be extracted from the standard echocardiogram.

As ultrasonic imaging of cardiac structures becomes increasingly used in diagnosis and research, there is greater desire for rapid computerized analysis of the information contained in an echocardiogram. The central problem with such computer analysis is transferring the relevant information into the computer. Current technology in automating echocardiography involves either digitizing the train of returning echoes in real-time or taking the information directly or indirectly from the graphic M-mode echocardiogram. Direct sampling of returning echoes requires a high speed analog to digital converter and other specialized hardware[1] since digitizing rates are usually as high as 4 or 5 megahertz. Taking information directly from a graphic echocardiogram involves a special scanning device[2] that automatically scans the echocardiogram, translating the image into an array of digitized values and sending the information to the computer. Taking graphic information indirectly from the echocardiogram is illustrated by a semiautomated approach[3] in which cardiac structures are traced by hand on transparent paper and then the traced record is converted to a video signal that in turn is converted to analog form by analog computer techniques.

These methods require not only sophisticated and expensive hardware to capture and enter the data into the computer, but also, in the first two cases, sophisticated computer software to enable the recognition of echocardiographic landmarks, such as various points on the mitral valve slope.

Design

We have demonstrated that less complex equipment may be used in computer-aided analysis of echocardiograms. Useful information can be taken from an M-mode echocardiogram and entered into the computer for instant analysis using a sonic digitizing tablet (Graf/Pen, Science Accessories Corporation). This device converts a point located manually with the digitizing pen into numerical

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X,Y coordinates (Fig. 1). The Graf/Pen has its own ASCII (American Standard Code for Information Interchange) interface which, when connected to an interactive computer terminal, can communicate over a standard telephone line with the DECSYSTEM-10, a time-shared computer system in the Medical Computing Resources Center at the University of Texas Health Science Center at Dallas. With this system, a technician can dial the computer using the standard telephone network, initiate the computer program from the interactive keyboard terminal and begin using the sonic pen to digitize important points directly from the echocardiogram. Most variables can be taken from the echocardiogram using relatively few points. Calculated results are immediately typed by the computer and stored on disk for future studies.

In comparison with the automatic scanning and real-time sampling techniques, this method requires more human involvement (a knowledgeable technician is needed to locate the desired points in the echocardiogram). This is not necessarily a disadvantage considering that human judgment in locating various landmarks may be as accurate, or more accurate, as some computer algorithms. Thus the accuracy of the measured variables depends on the quality of the echocardiogram and the ability of the technician to locate accurately the required landmarks. Our procedure, utilizing the sonic digitizer, has no control over the quality of the echocardiogram. However, it does lessen human error by freeing the technician from slow hand calculations and allowing him to average rapidly values from several cardiac cycles.

Computer Procedure

Once the computer connection is established by telephone, the technician can begin to execute the program. The first step is to calibrate distance and time in the echocardiogram by digitizing two points on the horizontal time axis and two on the vertical distance axis. The computer accepts the data and calculates the proper calibration factors.

Mitral valve closure: The velocity of mitral valve closure can be obtained by digitization of two points (E and F, Fig. 2). An averaging routine is available that obtains many velocities from the same echocardiogram and then determines the average velocity. This is exemplified by the dialogue shown in Figure 3. (All underlined characters represent those typed by the technician; all other text was produced by either the computer or the sonic digitizer.)

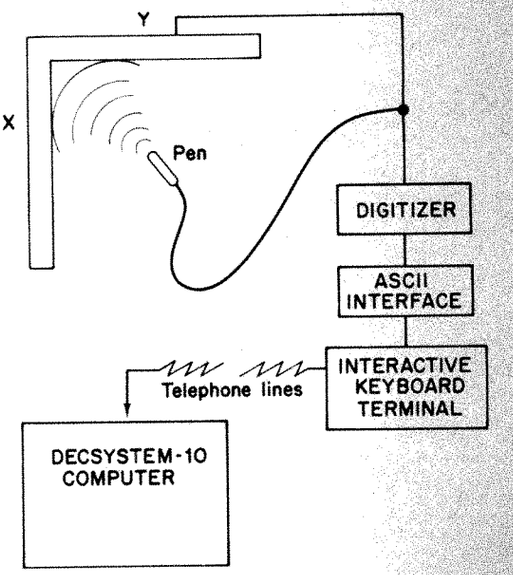

FIGURE 1. Diagram of sonic digitizer and ASCII (American Standard Code for Information Interchange) interface, and connection by telephone lines to remote time-sharing computer.

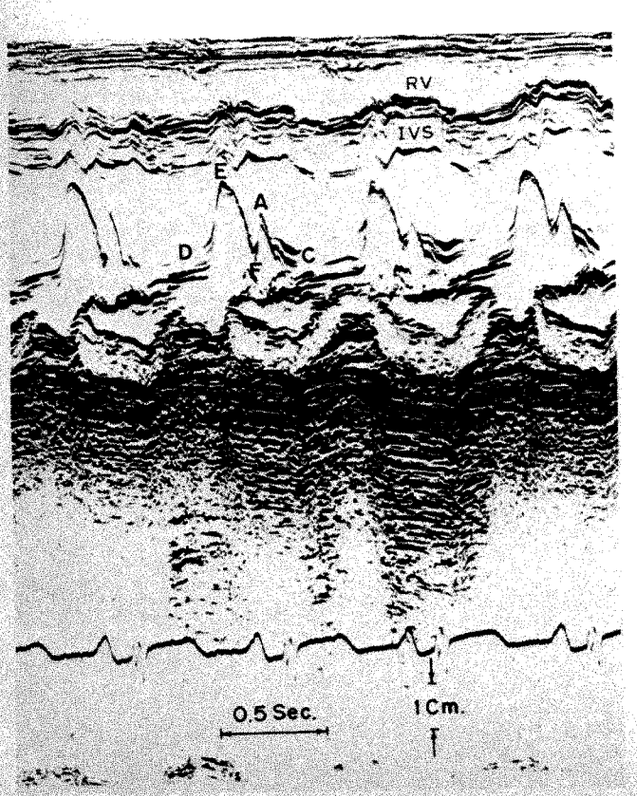

FIGURE 2. Original echocardiogram showing mitral valve motion. IVS = interventricular septum; RV = right ventricle.

```
.RUN GPEN
COMMAND:  CAL  VEL  VOL?  CAL

CALIBRATE 1 CM:
0593,0796
0595,0820
DISTANCE CAL=.04152

CALIBRATE 1 SEC:
0465,0796
0593,0796
TIME CAL=.00781

COMMAND: CAL  VEL  VOL?  VEL
*0284,0815
0302,0795
VELOCITY= 59.055 MM/SEC.
*0404,0817
0422,0795
VELOCITY= 64.960 MM/SEC.
*0528,0813
0544,0797
VELOCITY= 53.149 MM/SEC.
* -9

AVERAGE OF 3 VELOCITIES = 59.055 MM/SEC

COMMAND: CAL  VEL  VOL?
```

FIGURE 3. Sample of computer-technician dialogue in obtaining mitral valve velocity.

The program, GPEN, is started by typing "RUN GPEN," upon which the computer responds with "COMMAND:," asking if the operator wishes to CALibrate, obtain VELocity or VOLume. In the example, because the technician wishes to calibrate, he types "CAL" and the computer responds asking for 1 cm distance calibration. The technician then places the tip of the sonic pen (Fig. 1) on each point representing 1 cm distance in the echocardiogram (Fig. 2). These coordinates are automatically typed on the terminal as they enter the computer. The computer calculates a distance calibration factor and asks for two points representing 1 second (Fig. 2). Again the technician, with a touch of the sonic pen, enters these points into the computer, which then calculates the time calibration factor. These calibration values are retained by the computer for use in future calculations.

Next, the computer returns to the "COMMAND:" query to prompt the next request. The technician types "VEL" for velocity, to initiate the velocity routines, and the computer responds with the prompting character"*." With the sonic pen, the technician touches two points (for example, points E and F, Fig. 2), automatically entering the coordinates into the computer. The computer responds with the calculated velocity in units of millimeters per second. The computer types another "*" asking for two more points. Velocity points from two more cardiac cycles (Fig. 2) can then be entered as shown in the dialogue. Finally, when the sequence is to be terminated, the technician types "-9," signaling the computer to average the previously calculated velocities and type the results. The computer then returns to the "COMMAND:" query to await further instructions.

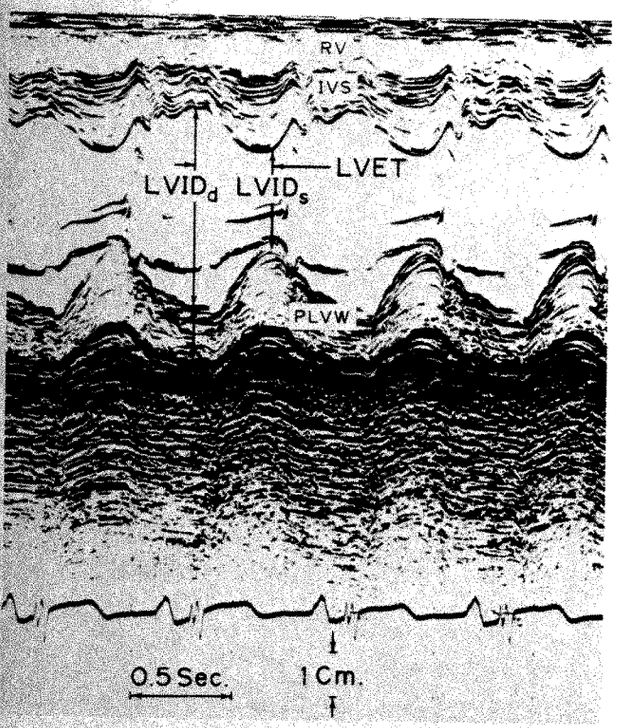

FIGURE 4. Original echocardiogram showing left ventricular cavity. IVS = interventricular septum; LVET = left ventricular ejection time, measured as recommended by Cooper et al.[8] $LVID_d$ = end-diastolic left ventricular internal diameter; $LVID_s$ = end-systolic left ventricular internal diameter; PLVW = posterior left ventricular wall; RV = right ventricle.

Left ventricular dimensions: These dimensions are obtained by the same technique. Two point digitization of the end-diastolic internal diameter (LVID-D), the end-systolic internal diameter (LVID-S), wall thickness and systolic ejection time may be done serially in the same echocardiogram (Fig. 4) and average values obtained. With this information, end-diastolic (EDV) and end-systolic (ESV) volumes using three methods,[4–6] left ventricular (LV) mass[7] and the velocity of circumferential fiber shortening (CIR. FIB. SH.)[8] are immediately typed. This is exemplified by the dialogue in Figure 5.

After the "COMMAND:" query, "VOL" is typed and the volume portion of the program is initiated. The specific gravity of cardiac muscle is requested and entered. Then the points associated with wall thickness are requested and entered. Figure 5 shows three sets of points from Figure 4 being entered

```
COMMAND: CAL  VEL  VOL? VOL
SPECIFIC GRAVITY = 1.05

ENTER WALL THICKNESS
*0455,0859
0454,0828
*0571,0860
0568,0830
*0689,0860
0686,0829
* -9
AVERAGE WALL THICKNESS = 1.338 CM.


ENTER LVID-D
*0458,0986
0457,0859
*0573,0985
0572,0859
*0693,0985
0690,0859
* -9
AVERAGE LVID-D = 5.493 CM.

ENTER LVID-S
*0515,0972
0514,0882
*0628,0972
0626,0883
*0744,0972
0742,0883
* -9
AVERAGE LVID-S = 3.885 CM.

ENTER EJECTION TIME
*0457,0875
0516,0875
*0572,0874
0628,0877
*0690,0873
0744,0877
* -9
AVERAGE EJECTION TIME = 0.441 SEC.

POMBO METHOD
EDV= 165.775 MLS.      ESV=58.628 MLS.
STROKE VOL=107.1478 MLS.     EJECT FRACT= 0.64634
LV VOL= 153.007 MLS.      LV MASS= 160.657 GRAMS


FORTUIN METHOD
EDV= 171.110 MLS.      ESV= 62.585 MLS.
STROKE VOL= 108.525 MLS.      EJECT FRACT= 0.634

TEICHHOLZ METHOD
EDV= 147.013 MLS.      ESV= 65.300 MLS.
STROKE VOL= 81.713 MLS.      EJECT FRACT= .5558 MLS.
CIR. FIB. SH.= 0.665 CIRC./SEC.
```

FIGURE 5. Sample of computer-technician dialogue in obtaining left ventricular dimensions.

by means of the sonic pen. When the technician types "-9," the computer types the average wall thickness. The program continues, requesting left ventricular end-diastolic internal diameter, left ventricular end-systolic internal diameter and ejection time in a similar manner. Finally, all relevant data having been entered, end-diastolic and end-systolic volume, left ventricular volume and mass, stroke volume and ejection fraction are calculated and typed by the computer.

The sonic digitizing tablet is capable of operating at speeds of up to 960 characters/sec. However, it is used at the comfortable operating speed of 30 characters/sec. The complete digitizing time is rapid and, depending on the experience of the technician, usually takes 1 to 2 minutes. Thus, results can be obtained from the echocardiogram in a relatively short period of time.

Discussion

Because the extraction of quantitative information from the echocardiogram is usually a relatively laborious and time-consuming procedure, the use of various computer systems has been proposed.[1-3] The central problem with such computer analysis is that of transferring relevant information to the computer. The use of the sonic digitizer offers one solution to this problem.

A sonic digitizing tablet connected to a time-sharing computer has many advantages. It is a fast and economic way of obtaining calculated results from an echocardiogram. The system is easy to use and apply. It requires relatively inexpensive equipment and utilizes an existing computer facility. Its value lies in its ability to perform calculations instantly and return the results immediately, permitting many values over several cardiac cycles to be obtained and averaged. Although the information obtainable from the program described is confined to the mitral valve and left ventricular function, the program may easily be extended to include any quantitative dimensions that can be obtained from a complete and technically suitable echocardiographic study. Because the sonic digitizer is connected to a general purpose time-sharing computer system, it is easy to add complex calculations related to phenomena that might prove to be clinically useful. These data can easily be stored on disk and later correlated with further patient information.

Two points require emphasis: First, the accuracy of the system described depends upon the technical quality of the original echocardiogram. Computer-aided analysis cannot be accurate without tracings of good quality. Second, echocardiographic calculations of left ventricular volume and wall thickness are based on a derivation of the ellipsoid formula used to calculate angiographic volumes.[10] These calculations assume that the echocardiographic diameter of the left ventricle is equal to the minor diameter measured by biplane angiography and that the major diameter is twice the minor diameter. Thus the accuracy of the echocardiographic calculations is based upon the validity of these geometric assumptions.

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Monitoring Tissue Oxygenation of the Heart After Myocardial Revascularization

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A polarographic technique capable of simultaneous monitoring of myocardial tissue oxygen tension (MPO_2) and intramyocardial electrograms by way of the same electrodes has been developed. Initially, the method was evaluated in dogs to verify the appropriateness of the directional changes of MPO_2 in function of selected determinants of myocardial oxygen supply (regional coronary blood flow, arterial blood oxygen tension) and demand (heart rate, force of ventricular contraction). A combined reduction of MPO_2 and elevation of the S-T segment in the corresponding electrograms was observed only when a 50 percent or greater reduction of blood flow to the sampled area was effected.

Subsequently, in nine patients undergoing aortocoronary bypass surgery, MPO_2 was measured from 48 areas for 2 weeks postoperatively. In 11 normal and 31 revascularized areas, MPO_2 increased during the postoperative period. In four areas subsequently found to be supplied by occluded grafts, MPO_2 decreased from 12.7 ± 3.1 (mean ± standard error) to 10.1 ± 3.3 mm Hg ($P < 0.05$). In two areas, MPO_2 decreased during the 3rd postoperative day from 16 to 3 and from 14 to 4.2 mm Hg, respectively. This reduction was attended by a significant rise in the S-T segment of the corresponding electrograms. This finding preceded by 24 hours standard electrocardiographic evidence of myocardial infarction. This technique appears to be sensitive and reliable, and thereby capable of enhancing the management of patients during the high risk early postoperative period after coronary bypass surgery.

Myocardial ischemia, including myocardial infarction, has been reported to recur in 10 to 35 percent of patients undergoing coronary bypass surgery.[1–3] If ischemia is diagnosed in the reversible phase of injury, problems related to surgical technique and unbypassed lesions in coronary vessels can be recognized: hence, the importance of monitoring myocardial tissue perfusion during and immediately after revascularization.

Polarography has been used experimentally for some time to measure oxygen tension in various tissues, including those of the heart.[4–11] Because the technique deals directly with oxygen, the factor most closely related to circulatory adequacy,[12] and because it allows continuous monitoring for long periods, its clinical suitability appeared worth exploring. To circumvent many theoretical limitations and objections,[13] a method was developed that allowed simultaneous measurement of tissue oxygen tension and direct intramyocardial electrograms. An overall workable system was assessed in the laboratory and used in a group of patients.

Material and Methods

The Oxygen Electrode and Electronic Circuit

The principle of polarography is presented in Figure 1. When a constant voltage of −0.6 v is applied to a platinum electrode (measuring electrode) and

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a chlorinated silver electrode (reference electrode) in a medium containing oxygen in solution, reduction of oxygen takes place on the surface of the platinum, inducing a current in the circuit. At that voltage, a linear relation exists between the current and the concentration of dissolved oxygen.

In our system, the oxygen electrode (cathode) consisted of a Teflon®-coated 90 percent platinum, 10 percent iridium wire (Medwire Corporation, Mount Vernon, N. Y.) measuring 15 to 20 μ in diameter. The tip was exposed and given a platinum black coating, using a solution of 3 percent platinum chloride dissolved in 0.025 percent lead acetate. The wire was passed through a 23 gauge needle to facilitate insertion, and the tip was bent in the shape of a hook to anchor it to the tissue and prevent movement. The reference electrode (anode) consisted of a silver-silver chloride disc pellet. The electronic circuit was composed of the elements represented in Figure 2. In this system, the polarization voltage was measured and regulated at the input to a differential amplifier. The output potential of this corresponded to the difference between the desired polarization voltage of −0.6 v and the actual value, that is, to the oxygen tension (PO_2)-dependent reduction current. The simultaneously obtained electrogram was amplified by the same differential amplifier and linearized by passage through an alternating current coupling circuit, while it was eliminated from the oxygen reduction current signal by passage through a filter circuit. Consequently, the use of two filters, high and low pass, enabled one electrode to be used for both PO_2 and electrocardiographic signals. Moreover, application of one −0.6 v reference level for all PO_2 channels permitted electronic matching of electrodes to within 1 percent of each other.

Electrical safety was attained by the use of isolated leakage-monitored alternating current line power, isolated direct current polarographic power, isolated input monitoring equipment and heavy local grounding to all exposed surfaces. Before each study, safety testing was performed to ensure that grounding, leakage and isolation were within acceptable safety standard limits (National Electrical Code, 1975, NFPA no. 70-1975, Boston, Mass.).

A calibration curve of each electrode was obtained in vitro by testing the response to various known concentrations of oxygen in 0.9 percent saline solution at a constant temperature of 37 °C (Fig. 3). Electrodes that failed to respond in linear fashion were discarded. The effect of 1 hydrogen-ion con-

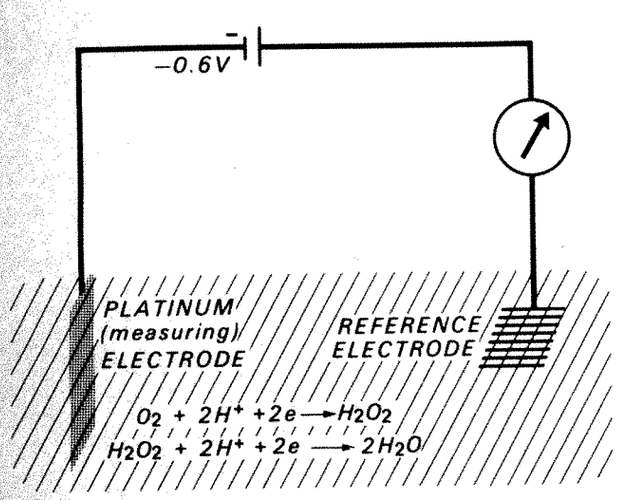


FIGURE 1. Principle of polarography. (See text for description.)

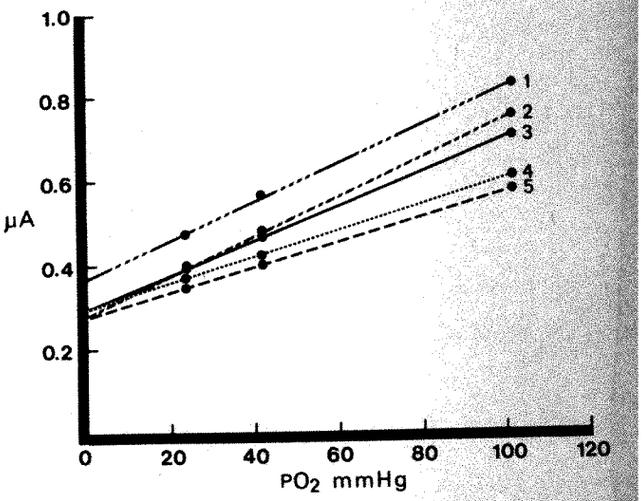
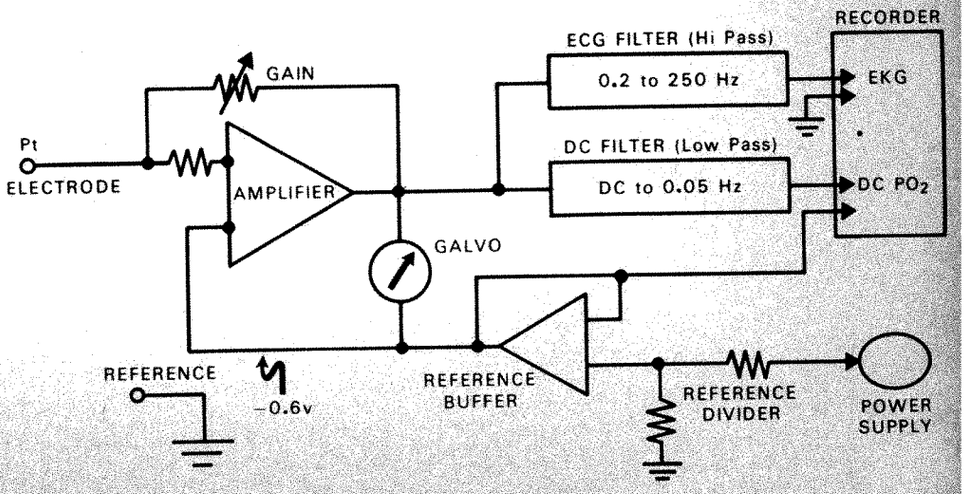


FIGURE 3. Calibration of the oxygen electrode in vitro. Numbers 1 to 5 at right refer to individual electrodes calibrated by comparing electrical current (μA) in relation to partial pressure of oxygen (PO_2) in saline solution.



POLAROGRAPH SCHEMATIC (Block Diagram)

FIGURE 2. Electronic circuit for simultaneous measurement of myocardial tissue oxygen tension and intramyocardial electrograms. (See text for description.) DC = direct current; ECG and EKG = electrocardiogam; Galvo = galvonometer; PO_2 = partial pressure of oxygen; Pt = platinum.

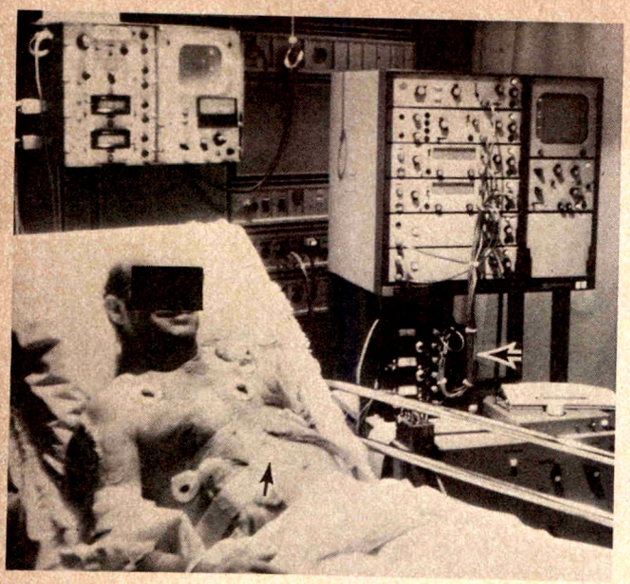


FIGURE 4. Clinical application of the polarographic method.

centration (pH) on the electrode system was also studied in vitro. The pH of the solution was varied, with use of gas mixtures containing 2 percent carbon dioxide, which maintained a pH of 7.2 to 7.3, or a bicarbonate-buffered solution equilibrated with room air, which produced a pH of 7.8 to 7.9. Tests were carried out with six electrodes to determine whether the oxygen current would be affected. At a constant PO_2 level, over a pH range of 7.2 to 7.9, differences in oxygen current in the various solutions were within 0.2 percent. This observation is in agreement with the findings of others.[4,5,13]

Studies in Dogs

Initially, experiments were performed to verify the appropriateness of the directional changes measured by the polarographic system. Mongrel dogs, weighing 20 to 30 kg, were anesthetized with sodium pentobarbital, 30 mg/kg intravenously. After institution of mechanical ventilation, the heart was exposed through a left lateral thoracotomy and suspended in a pericardial cradle. Each animal received sodium heparin, 6,000 units, and lidocaine hydrochloride at an infusion rate of 2 mg/min. Arterial blood pH, PO_2 and partial pressure of carbon dioxide (PCO_2) were determined intermittently using a blood gas analyzer (Instrumentation Laboratory, Boston, Mass.). Respiratory adjustments were made when necessary to keep blood gasses within physiologic ranges. The central aortic pressure was measured by means of a large bore polyethylene catheter inserted into the femoral artery and connected to a Statham P23db transducer. Coronary blood flow was monitored with the aid of two electromagnetic flow probes, one placed round the proximal left circumflex coronary artery and one on the left anterior descending coronary artery in its mid-portion. The flow probes were connected to a Biotronex multichannel flowmeter. Zero flow was repeatedly mechanically determined during the course of each experiment.

A micrometer-adjusted ligature was placed immediately distal to the arterial flow probe to produce localized myocardial ischemia of various degrees. Left ventricular contractile force and wall tension were determined with use of a Walton-Brodie strain gauge arch of 120 ohms resistance, implanted parallel to the long axis of the superficial cardiac muscle fibers supplied by the left anterior descending coronary artery distal to the snare ligature. Multiple platinum electrodes were inserted at depths of approximately 2 mm (subepicardial) and 7 mm (subendocardial) in the same area. The reference electrode was implanted subcutaneously in the right hind leg. All observations were displayed on an Electronics for Medicine DR-8 high fidelity recording system.

In 13 dogs, control observations were recorded approximately 30 minutes after electrode implantation and the sensitivity of the polarographic system to changes in regional coronary blood flow was tested by producing progressive micrometered-ligations resulting in reductions of flow of 10, 50 and 100 percent of baseline value. Data were obtained 2.5 and 5 minutes after each constriction. Factors other than perfusion known to alter tissue oxygen tension were also examined. Thus, the effects of ventilation with 100 percent oxygen versus room air were studied in five dogs; the effects of an infusion of isoproterenol, 2 μg/min, which is known to increase myocardial oxygen consumption, were studied in five dogs.

Second, experiments were conducted for the purpose of standardization of the method. Since changes in the oxygen content of a venous effluent are generally considered to reflect directional changes in tissue oxygenation, PO_2 of venous blood was obtained from the sampled area. With use of the same preparation, a ligature was placed on the left anterior descending coronary artery and a Teflon® cannula was inserted in the concomitant vein. Multiple electrodes were implanted in the area supplied by the distal artery. Coronary venous blood was allowed to flow continuously into a beaker from which it was returned to the animal by way of the jugular vein. Blood sampling for the measurement of PO_2 was obtained at predetermined intervals directly from the cannula. Observations were made in three dogs under various conditions: ventilation with room air or mixtures of 6, 40 or 80 percent oxygen, and during partial and complete occlusion of the left anterior descending coronary artery. In all, 50 recordings were made.

Statistical significance of changes was tested using the paired Student's t test. The relation of myocardial PO_2 to coronary venous PO_2 was studied by regression analysis.

Human Application

In nine patients undergoing myocardial revascularization, myocardial tissue oxygen tension and myocardial electrograms were recorded from 48 different areas. The sites for monitoring were chosen on the basis of previous assessment by coronary arteriography. They were classified "ischemic," if supplied by a major vessel with more than 75 percent obstruction of its proximal course, or "normal," if supplied by a vessel with less than 50 percent obstruction and if ventriculography showed the corresponding segmental contraction pattern to be normal. The electrodes were implanted after completion of the aortocoronary bypasses. The wires were wrapped in a Penrose drain and passed through the lower end of the sternotomy wound to reach the polarograph (Fig. 4). The reference electrode was attached with conductive gel to the lower right leg.

Myocardial tissue oxygen tension (MPO_2) and electrograms were monitored continuously in the operating room and recorded approximately every 6 hours for up to 2 weeks in the intensive or intermediate care unit. At the end of this period, coronary arteriographic and left ventriculographic studies were repeated, and the electrode wires were pulled out. On the basis of these studies, the sampling sites were designated "normal," if the area was again noted to be supplied by a normal or significantly obstructed coronary artery, "revascularized," if the area was supplied by a patent vein graft, or "ischemic," if the vein graft had occluded.

Two weeks after coronary bypass surgery and immediately after repeat coronary arteriography, the electrodes were in-

dividually removed by gentle tugging on the distal end. While the electrodes were being removed, simultaneous oscilloscopic monitoring of the heart rhythm showed no premature ventricular contractions or other signs of arrhythmia. The electrode extraction was accomplished without discomfort, and no bleeding or subsequent complications were evident.

Results

Canine Studies

Subepicardial PO_2 had a much wider range than subendocardial PO_2 under normal conditions and after various interventions. Attention was therefore focused on subendocardial PO_2, which measured 11.5 ± 1.5 mm Hg under normal conditions.

The S-T segment of each electrogram was elevated upon electrode implantation. It tended to decline progressively and then stabilize (usually within 30 minutes) to the level of 0.25 ± 0.1 mm above the isoelectric line.

Subendocardial PO_2 decreased with progressive reductions of coronary blood flow (Table I). With a 10 percent reduction of flow, MPO_2 decreased an average of 11.3 percent, whereas no change occurred in functions known to affect myocardial oxygen consumption, that is, heart rate, contractile force or wall tension. With a 50 percent reduction of flow, MPO_2 decreased an average of 36.7 percent (Fig. 5); although there was no change in heart rate or blood pressure, paradoxic systolic distension of the ischemic left ventricular segment occurred and there was an average 346 percent increase in wall tension. Total occlusion of the left anterior descending coronary artery caused a further average 60 percent reduction in MPO_2. Heart rate and systemic blood pressure were not affected over the time interval studied, but paradoxic systolic expansion of the ischemic segment increased wall tension an average of 1,612 percent. Collateral blood flow, estimated from the increase in left circumflex coronary arterial flow, showed no change with a 10 percent reduction in left anterior descending coronary arterial blood flow but manifested an average increase of 18 and 20 percent, respectively, with blood flow reductions of 50 and 100 percent. The electrograms showed no changes of "injury" with a 10 percent reduction of flow, but 50 and 100 percent reductions produced significant elevations of the S-T segment (Fig. 6).

With the administration of isoproterenol, heart rate and contractile force, each a major determinant of myocardial oxygen consumption, increased an average of 15.5 percent (heart rate from 142 ± 6 to 164 ± 9 beats/min; $P < 0.001$). With coronary blood flow unchanged, these alterations produced an average 23.6 percent reduction in MPO_2 (from 12.1 ± 1.1 to 9.2 ± 1 mm Hg; $P < 0.05$), but no elevation of the S-T segment occurred.

After ventilation with 100 percent oxygen, a sevenfold increase in arterial PO_2 produced a significant increase in MPO_2 (from 11.5 ± 1 to 14.6 ± 1 mm Hg; $P < 0.05$). Conversely, modifying ventilation from 100 percent oxygen to room air produced an immediate reduction in MPO_2. This, again, was not attended by ischemic changes in the electrograms.

Thus, a significant decrease in MPO_2, concomitant with a significant elevation of the S-T segment in the corresponding electrograms, was produced only by a major (50 percent or more) reduction in blood flow supplying the sampled area.

TABLE I

Effects of Three Levels of Reduction of Coronary Blood Flow on MPO_2 and Myocardial Electrograms (mean values ± standard error)

	Level 1		Level 2		Level 3	
	Control	10% Reduction	Control	50% Reduction	Control	100% Reduction
LAD flow (ml/100 g LV/minute)	40 ±5	36 ±3*	42 ±2	21 ±2*	40 ±3	0*
Subepicardial MPO_2 (mm Hg)	15.0 ±5.2	14.1 ±4.9	16.1 ±5.9	10.9 ±5.8	15.4 ±5.2	7.5 ±2.9*
S-T elevation (mm)	0.27 ±0.0	0.25 ±0.1	0.28 ±0.0	4.9 ±0.8*	0.25 ±0.1	16.0 ±3.0*
Subendocardial MPO_2 (mm Hg)	11.5 ±0.5	10.3 ±0.2*	10.8 ±1.1	6.8 ±1.1*	10.9 ±1.0	3.4 ±1.0*
S-T elevation (mm)	0.25 ±0.1	0.25 ±0.1	0.23 ±0.03	6.2 ±1.3*	0.25 ±0.05	18.0 ±2.0*
Heart rate (beats/min)	150 ±5	...	150 ±5	...	150 ±5	...
Mean aortic pressure (mm Hg)	105 ±5	...	105 ±5	...	105 ±5	...
% Passive systolic distension (dyskinesia)	0	0	0	346 ±20*	0	1612 ±340*

* Statistically significant difference from control value ($P < 0.05$).
LAD = left anterior descending coronary artery; MPO_2 = myocardial tissue oxygen tension.

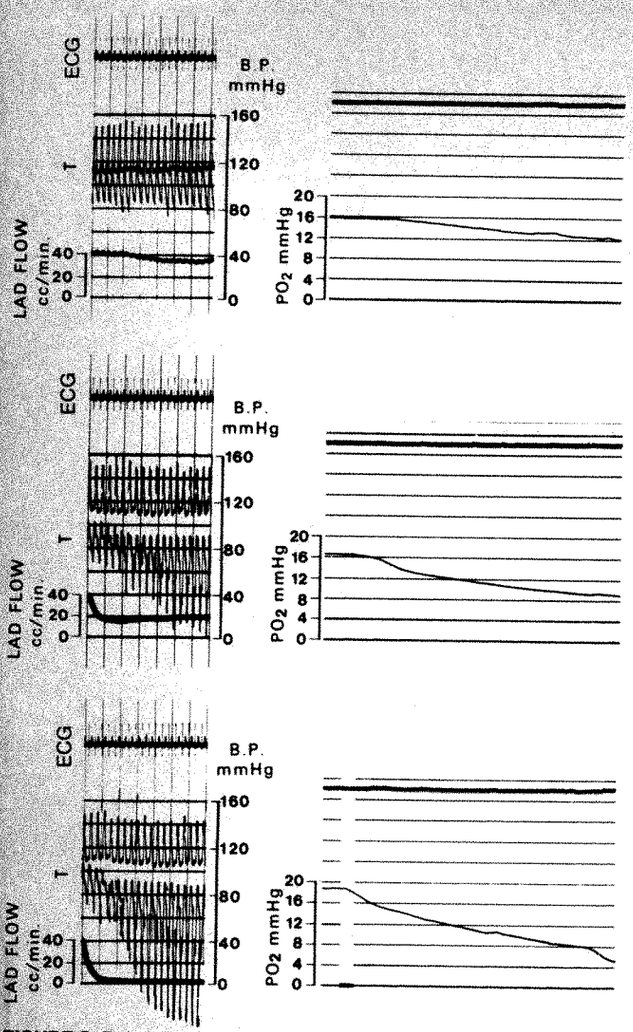


FIGURE 5. Relationship of myocardial tissue MPO_2 to various degrees of reduced regional coronary blood flow. Each panel shows the standard (lead II) electrocardiogram (ECG), aortic blood pressure (B. P.) with a scale 0 to 160 mm Hg, wall tension (T), mean left anterior descending (LAD) coronary blood flow with a scale of 0 to 40 ml/min, and myocardial tissue MPO_2 with a scale 0 to 20 mm Hg. **Top panel,** a 10 percent reduction in blood flow produces a reduction of myocardial tissue MPO_2 without changes in heart rate, pressure or tension. **Middle and lower panels** 50 and 100 percent reductions in blood flow produce proportionate decreases in myocardial tissue MPO_2 and changes in wall tension.

Coronary venous blood PO_2 (VPO_2) measured 19 ± 1 mm Hg under normal conditions and room air ventilation. A linear relation was found between MPO_2 and VPO_2 under a variety of conditions (Fig. 7).

Human Studies

Myocardial oxygen tension was measured from 48 areas in nine patients (Table II). Eleven areas were supplied by coronary arteries that were not bypassed because they were considered normal or minimally diseased in preoperative arteriographic studies; 37 areas were supplied by bypassed arteries. The first valid reading, for purpose of the study, was taken upon return of the patient to the cardiac intensive care unit; subsequent readings were taken at approximately 6 hour intervals for 2 weeks. The data are tabulated using four time intervals: T_1 (the first reading in the intensive care unit); T_2 (the end of the immediate postoperative period—24 hours); T_3 (the end of the intermediate period—1 week); and T_4 (the end of the total period of observation). MPO_2 from the 11 "normal" areas was 10 ± 1.7 mm Hg at T_1 and gradually increased with time to 17.1 ± 2.1. MPO_2 from the 37 revascularized areas was 14 ± 2.4 mm Hg at T_1. This value was moderately but significantly ($P < 0.05$) higher than in the nonrevascularized areas. Subsequent measurements showed

TABLE II

Myocardial Tissue Oxygen Tension (MPO_2) After Revascularization (mean ± standard error)

	Nonrevascularized Areas (mm Hg) (no. = 11)	Revascularized Areas (mm Hg) (no. = 37)		
		A (no. = 31)	B (no. = 4)	C (no. = 2)
T_1	10 ± 1.7	14 ± 2.4 (all groups)		
T_2	15.2 ± 1.2*	15.4 ± 1.6	12.7 ± 3.1	16; 14
T_3	16 ± 2	17 ± 1.2	11.5 ± 2.7	3; 4.2
T_4	17.1 ± 2.1*	19.5 ± 1.9*	10.1 ± 1.3*	

* Statistically significant change ($P < 0.05$) from previous time interval.

A = revascularized areas with patent vein grafts on postoperative study; B and C = revascularized areas with occluded grafts on postoperative study (in C, the decrease in MPO_2 was attended by S-T elevation in the corresponding electrograms); T_1 = first reading in the surgical cardiac intensive care unit; T_2 = end of the immediate postoperative period (24 hours); T_3 = end of the intermediate period (1 week); T_4 = end of the total period of observation (2 weeks).

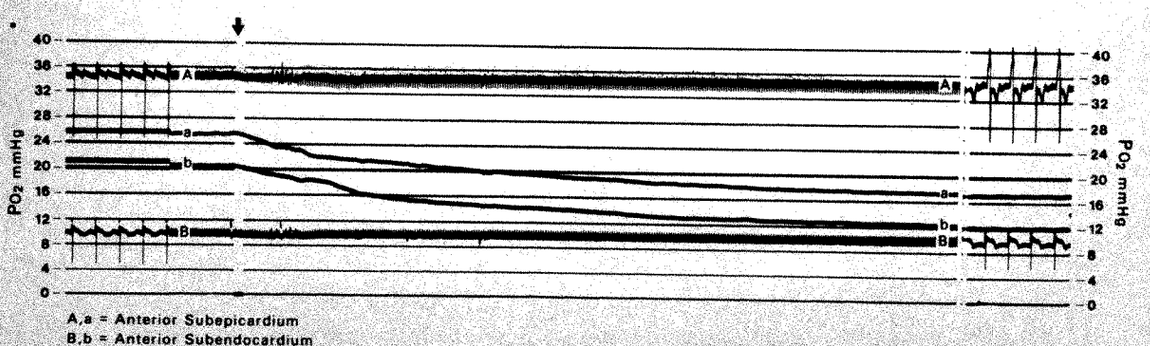


FIGURE 6. From the top down: **(A)** the electrogram and **(a)** the MPO_2 tracing from the subepicardial electrode; **(b)** the MPO_2 tracing and **(B)** the electrogram obtained from the subendocardial electrode implanted in the same microarea. Under control conditions, subepicardial MPO_2 is greater than subendocardial MPO_2. After occlusion of the left anterior descending coronary artery **(at arrow),** there is an immediate drop in both tension curves. After 2.5 minutes, significant S-T elevation is evident in the subendocardial electrogram **(B).**

one of three trends: (1) a consistent gradual increase (31 areas); (2) a moderate although significant decrease with no change in the myocardial electrograms (4 areas); or (3) a sudden decrease, with S-T elevation in the electrograms (2 areas). Arteriographic data at the end of 2 weeks validated the changes observed in tissue oxygen tension. Thus, visualization of the nonbypassed arteries showed no change from the preoperative status. Visualization of blood supply to areas with increasing oxygen tension revealed patent vein grafts, that to areas with reduced oxygen tension revealed occluded grafts. Ventriculography, by demonstrating akinetic segments, confirmed the occurrence of myocardial infarction only in the two areas that had a sudden severe reduction in MPO_2 attended by electrographic changes.

The sensitivity of our monitoring system was indicated further by the observation in one patient of a decrease in MPO_2 in association with ischemic S-T elevations after the injection of dye during postoperative coronary arteriography (Fig. 8). An unanticipated by-product of the monitoring technique occurred during postoperative observation of another patient who underwent emergency myocardial revascularization for threatened extension of an anterior wall myocardial infarction. In this case, the postoperative standard electrocardiogram showed Q waves and S-T elevations consistent with an active evolving anteroseptal infarct (Fig. 9). However, the direct myocardial electrograms did not show significant S-T displacement, and MPO_2 did not decrease in the area presumed to be ischemic. Postoperatively, arteriography revealed a patent vein graft supplying a muscle segment whose contraction pattern had been restored toward normal. Hence, our method was effective in distinguishing between S-T

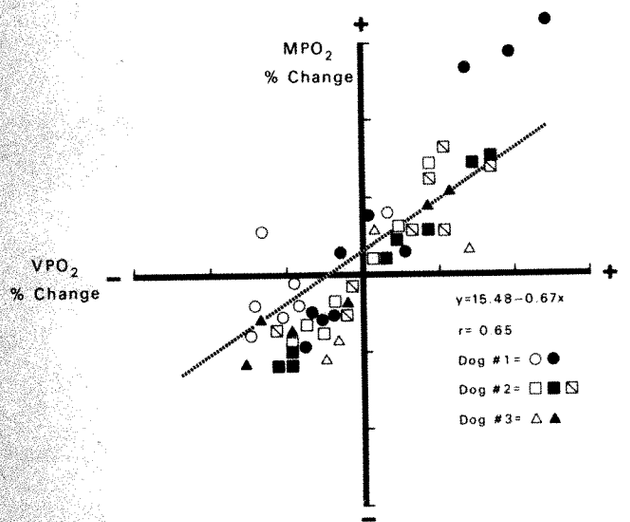


FIGURE 7. Regression line representing the relation of myocardial tissue PO_2 (MPO_2) to coronary venous PO_2 (VPO_2) in three dogs.

FIGURE 8. Postoperative angiogram with visualization of a vein graft to the right coronary artery **(large arrow). Small arrows** indicate three pairs of platinum electrodes implanted, one subepicardially and one subendocardially, in the anterior, lateral and posterior walls of the left ventricle. Injection of dye through the graft with retrograde visualization of the left anterior descending coronary artery produced a reduction in MPO_2 in the area supplied by this vessel.

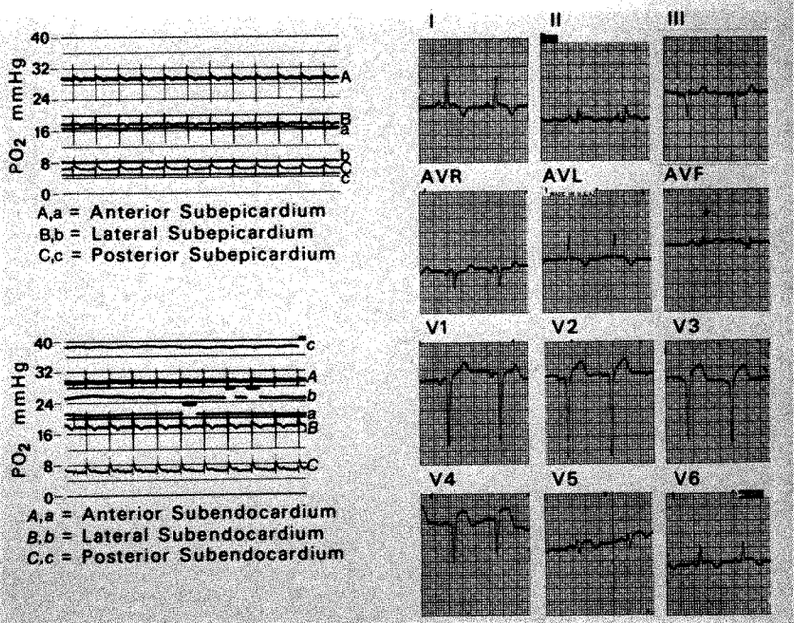


FIGURE 9. The high MPO_2 level with no S-T elevation on the anterior wall of the left ventricle contrasted with the standard electrocardiographic changes suggesting an anteroseptal infarct in evolution. The patient proved to have postoperative pericarditis rather than myocardial infarction.

segment shifts due to postoperative pericarditis and those of acute myocardial ischemic injury.

Analysis of electrode performance: The sensitivity of each electrode was tested in each patient before each observation by determining its response to 100 percent oxygen inhalation. In 48 of 54 electrodes, an increase in arterial blood PO_2 of 76.1 ± 17.2 mm Hg resulted in an increase in MPO_2 of 6.3 ± 0.9 mm Hg ($P < 0.05$). In 6 of 54 electrodes, a very low level of myocardial oxygen tension was attended by a more than 50 percent loss of electrographic voltage. This change was subsequently found to be due to breakage of the electrode tip.

The question of electrode "poisoning" as a function of time was examined by determining on 2 consecutive days the rate of myocardial tissue oxygen tension change per unit of increase in arterial blood PO_2 during the first 3 minutes of oxygen inhalation. The average response on the first day was

$$\frac{0.41 \text{ mm Hg/sec } MPO_2 \times 10^3}{\text{mm Hg arterial } PO_2} \pm 0.04$$

This response did not change significantly on the following day.

Discussion

Since the advent of coronary bypass surgery, it has become important to gauge the adequacy of restoration of blood flow in all regions of the myocardium. A prognostic value is now attached to measurements of flow through the grafts as a result of the observation[14] that mean flow values of less than 20 cc/min are associated with a high rate of graft occlusion. However, these data are obtainable only during the limited time available in the course of the total surgical procedure. Consequently, information is recorded that may not pertain to subsequent postoperative clinical circumstances. Moreover, measured graft flow does not necessarily indicate delivery of oxygen to specific sites of ischemic cardiac muscle. Postoperatively, the effects of revascularization, or changes in its status, are conventionally monitored with electrocardiograms, serum enzyme determinations and measurement of hemodynamic variables. However, with these methods the diagnosis of myocardial ischemic injury is made with great difficulty, usually when infarction has already occurred.[1-3]

Problems and limitations of polarography: A method capable of monitoring myocardial tissue oxygenation on a continuous basis and for an adequate period of time would thus be of definite advantage. Polarography, developed through the work of Heyrovsky,[15] is theoretically such a method. However, because of its theoretical limitations few investigators have attempted a clinical use. There are three main problems:

1. *Problems related to the oxygen electrode:* The electrode must be small, atraumatic, resilient enough to prevent breakage and shaped so as to allow no movement. Results of calibration in vitro, under predetermined conditions where the oxygen diffusion is stable, cannot apply to an in vivo situation, particularly in the beating heart, where a variety of changing factors tend to alter that electrical field continuously. A significant problem with the oxygen electrode has been reported to be the progressive decrease in sensitivity ("aging" or "poisoning") attributed to changes in pH toward alkalinity in the area close to the electrode with resulting precipitation of insoluble salts upon the electrode surface.[13]

2. *Problems related to the medium:* Changes in temperature, pH and osmolarity tend to affect the solubility and diffusion coefficient of oxygen. Furthermore, with reference to the heart, there is a stirring effect that is variable and uncontrollable.[13]

3. *Problems related to the determinants of tissue oxygen tension:* According to Krogh's equation,[16] the physiologic factors that determine local oxygen tension are many, some uncontrollable: arterial blood oxygen tension, perfusion pressure and blood flow, oxygen consumption, geometric configuration of the tissue, capillary density, capillary radius and length and diffusion distance.

However, not all of these factors are equally important and some of these problems can be circumvented. Thus, wide ranges in pH and osmolarity were found to have little practical effect on the polarographic current,[4,5,13] as confirmed by our observations in vitro. Temperature must be taken into account when the oxygen electrode is implanted under conditions of hypothermia, but a correction factor is available.[5] Clark et al.[17] corrected the problem of "aging" of the platinum electrode by constructing a membrane-covered tip. However, the importance of this problem has been questioned,[11] particularly when measurements are made to establish relative changes rather than absolute values. Our observations confirm that, over relatively short periods, the bare tip electrode responds satisfactorily to changes in tissue oxygen tension.

Experimental verification of method: We chose to use a bare tip platinum electrode because of its small size and simple design and the need to minimize tissue trauma. Each electrode was calibrated in vitro before use by exposure to different known concentrations of oxygen in solution. Electrodes that failed to respond to these changes in a linear manner were discarded. The system was standardized in vivo by comparing tissue oxygen tension levels, as measured by several electrodes, with the oxygen tension of the venous blood effluent from the sampled area under various conditions. We did so, because of the relative ease with which local venous coronary blood can be sampled and since it is generally assumed that the PO_2 of this blood reflects myocardial tissue oxygenation.[18] That blood PO_2 was always greater than tissue PO_2 can be explained on the basis of Kety's equation[19] showing that tissue oxygen tension equals capillary oxygen tension minus a coefficient calculated from the relation of capillary radius to tissue cylinder radius, tissue oxygen consumption and oxygen diffusion factor. The linear relation between these two measurements supported the contention that relative changes in each electrode's measurement reflected changes in the oxygenation of the sampled tissue.

In this context, the results of our studies in dogs show that a significant change in polarographic current can

be measured after a minimal (10 percent) reduction in regional coronary blood flow. In addition, without changing regional perfusion but primarily augmenting factors known to increase myocardial oxygen consumption, a significant current reduction was likewise demonstrated. Not until coronary occlusion produced obvious segmental abnormalities of cardiac muscle contraction did the decrease in myocardial tissue oxygen tension accompany ischemic changes in the local electrograms. After verification in the experimental animal, the method was transferred from laboratory to clinical application. For clinical purposes, a reduction in MPO_2 would not be considered significant unless attended by a simultaneous elevation of the S-T segment in the corresponding electrogram.

Clinical applications: Our observations in patients were consistent with those made in the laboratory. Thus, a significant decrease in oxygen tension was noted in the areas subsequently found to have occlusion of the serving vein graft. In contrast, MPO_2 levels increased when the grafts remained patent. Moreover, in two patients whose postoperative ventriculogram confirmed the new development of myocardial infarcts a sudden severe reduction in MPO_2, attended by S-T elevation in the corresponding electrogram, preceded by 24 hours the development of new Q waves in the standard electrocardiogram.

Clinical sensitivity of the method for periods up to 2 weeks was proved when postoperative coronary arteriography unintentionally evoked myocardial ischemia coincident with an abrupt decrease in MPO_2. Vasli[20] reported analogous findings using polarography to study tissue oxygen tension in the human calf muscle after the injection of dye in a prosthetic graft. Thus, the correlation between polarographic-electrographic changes and postoperative angiographic studies indicates that this method is adequate to monitor tissue perfusion after revascularization. Furthermore, satisfactory performance for a period of 2 weeks enhances its value, since most perioperative myocardial infarctions occur at surgery or within the first few postoperative days.[21,22]

In conclusion, polarography combined with simultaneous recording of myocardial electrograms appears to be a valid and practical method for monitoring myocardial tissue perfusion after revascularization. The described improvements in the design of the polarographic system and the simplicity of application have been effective in converting this method from one of primarily experimental use to one suitable for clinical study.

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A General Cardiovascular Risk Profile: The Framingham Study

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Persons at high risk of cardiovascular disease can be effectively identified from a measurement of their serum cholesterol and blood pressure, a smoking history, an electrocardiogram and a determination of glucose intolerance. One general function for identifying persons at high risk of cardiovascular disease is also effective in identifying persons at risk for each of the specific diseases, coronary heart disease, atherothrombotic brain infarction, hypertensive heart disease and intermittent claudication, even though the variables used have a different impact on each particular disease.

The 10 percent of persons identified with use of this function as at highest risk accounted for about one fifth of the 8 year incidence of coronary heart disease and about one third of the 8 year incidence of atherothrombotic brain infarction, hypertensive heart disease and intermittent claudication. Hence the function provides an economic and efficient method of identifying persons at high cardiovascular risk who need preventive treatment and persons at low risk who need not be alarmed about one moderately elevated risk characteristic.

Of the relatively lethal diseases afflicting populations in the industrialized world the cardiovascular diseases are by far the most common. In the Framingham Study, the chances of developing a cardiovascular disease by age 65 are 37 percent for a man and 18 percent for a woman. There is some interest, then, in identifying persons at special risk of having cardiovascular disease and in specifying the characteristics that put them at high risk. This paper describes a single risk function for predicting several different cardiovascular diseases and evaluates its efficiency in identifying persons most likely to have these cardiovascular diseases and consequently most in need of preventive care.

Methods

Since 1948 the Framingham Study has followed up a sample of 5,209 men and women residing in Framingham, Mass. with use of clinical examinations, conducted every 2 years, and continuous surveillance of morbidity and mortality.[1] On each examination a variety of characteristics are measured, including blood chemistry values and blood pressure; an electrocardiogram is taken; and a thorough cardiovascular evaluation is made after obtaining a routine history and physical examination.

To be considered at risk for cardiovascular disease a person must have been free at the start of the study of coronary heart disease, congestive heart failure, cerebrovascular disease, intermittent claudication and rheumatic heart disease. In the following discussion, cardiovascular disease refers to this set of diseases exclusive of rheumatic heart disease. The criteria and methodology for determining the set of variables and the various cardiovascular diseases discussed in this paper are given elsewhere.[2]

A logistic regression model for conditional risk is assumed, that is, the probability that disease will be manifested in a specified time period given a set of variables $x_1, x_2, \ldots, x_j$ measured at the first examination is assumed to take the form $[1 + \exp - (b_0 + b_1x_1 + b_2x_2 \ldots b_jx_j)]^{-1}$ where b_0, b_1, b_2, and so forth are

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constants to be estimated from the data. Estimation is by the method of Walker-Duncan.[3]

Standardized coefficients are obtained by multiplying each b_i by the standard deviation of the variable x_i with which it is associated. These may be used to judge the relative importance of each of the variables in estimating the probability of each specific disease.

Results

Risk Factors

Individual risk factors: Many host and environmental contributors to cardiovascular disease have been identified. These are of various kinds: atherogenic personal attributes (serum cholesterol level, blood pressure and glucose intolerance, for example); living habits that promote these traits (inactivity and overeating) or carry a direct cardiovascular risk (cigarette smoking); signs of preclinical cardiovascular disease (including electrocardiographic abnormalities, cardiac enlargement on X-ray film, other evidence of impaired cardiac function). Many of these factors are common in the American population (Table I). There is a large body of epidemiologic evidence from a variety of populations concerning the relation of these characteristics to cardiovascular disease, particularly coronary heart disease in men. The evidence is remarkably consistent, with few exceptions, that these characteristics do distinguish persons at high risk from persons at low risk.[4]

Although one might use any of these characteristics singly to separate high and low risk persons in a population, the efficacy of such an approach would vary with the characteristic chosen and the cardiovascular disease for which risk was being assessed. The most useful single factor for detecting persons at high risk of cardiovascular disease would be blood pressure, since a large body of evidence indicates that it is the most potent antecedent to the cardiovascular diseases discussed here, although it is not equally important for all of these diseases. Using blood pressure to screen for persons at high risk of stroke would be quite effective. Some 57 percent of the incidence of atherothrombotic brain infarction at Framingham arises in the 19 percent of the population having a systolic blood pressure of 160 mm Hg or greater. The statistics for hypertensive heart disease are similar. On the other hand, high blood pressure is antecedent in a much smaller proportion of cases of coronary heart disease and an even smaller proportion of cases of intermittent claudication. Overall, 36.2 percent of cases of cardiovascular disease occurring in a 2 year period arise in the group of persons whose systolic blood pressure is greater than 160 mm Hg.[2]

While there is some convenience in dichotomizing a continuous variable like blood pressure into high and low, one would prefer some method to take into account the exact value. Within the range of systolic blood pressure values that physicians usually consider to be "within normal limits" (perhaps 100 to 140 mm Hg) there is a two-fold range in the risk of cardiovascular disease proportional to the systolic level (Fig. 1). The same applies to serum cholesterol; here, too, risk is proportional to level and there is no critical value to indicate where normal ends and abnormal begins. Overall, a logistic curve (which implies a steady increment of risk with increasing level) seems to fit the data for serum cholesterol and systolic blood pressure fairly well and to provide a rational procedure for taking the exact level into account (Fig. 1 and 2).

However, a single risk factor is neither a logical nor an effective means of detecting persons at high risk of cardiovascular disease. Screening efficiency can be considerably improved if other risk factors are taken into account. At any level of blood pressure the risk of cardiovascular disease varies from less than average to

TABLE I

Percent Prevalence of Selected "Risk Factors" in the United States

Age (yr)	Inactivity*	Obesity	Hypertension	Cigarette Smoking	Diabetes	Hyper-cholesterolemia	ECG-LVH*
				Men			
35–44	12.1	12.5	13.5	48.6	1.1	20.2	2.9
45–54	16.9	14.7	18.3	43.1	1.1	25.7	4.8
55–64	21.0	12.5	22.3	37.4	3.3	23.5	10.1
65–74	27.1	12.7	27.1	22.8†	3.2	21.6	7.1
				Women			
35–44	13.3	20.1	8.5	38.8	0.8	12.9	0.9
45–54	19.3	24.2	18.2	36.1	2.9	28.0	3.6
55–64	30.8	30.9	31.2	24.2	3.2	49.7	4.1
65–74	39.0	27.2	47.6	10.2†	6.1	51.0	9.6

* Framingham, Mass.

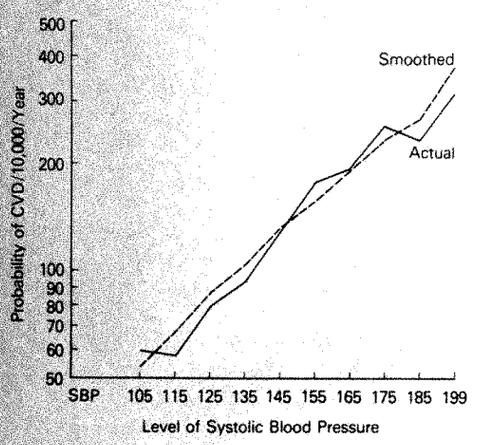
† Age 65 and over.

Definitions: Inactivity is average oxygen consumption less than 0.30 liter/min (1954–58); obesity is weight 20 percent or more above median (1960–62); hypertension is a blood pressure at least 160/90 (1960–62); cigarette smoking refers to current habits (1970); diabetes is medically treated (1960–62); hypercholesterolemia is a serum cholesterol at least 260 mg/100 ml (1960–62); ECG-LVH is an electrocardiographic pattern of left ventricular hypertrophy (1948–53). Data for 1960–62 come from publications of the Health Examination Survey, series 11, numbers 14 (obesity), 13 (hypertension), 2 (diabetes) and 22 (hypercholesterolemia). Data on cigarette smoking are from the National Center for Health Statistics (unpublished).

many times average depending on associated characteristics (Fig. 3).

Composite "risk function" score: The most efficient and sensible method of evaluating risk would appear to be to synthesize the major contributors to cardiovascular disease quantitatively into a composite score. This can be accomplished using a multiple logistic formulation that estimates the conditional probability of any major cardiovascular event for any set of risk factors (x), employing the actual level of each of the factors, their regression coefficients (b) and constants for the intercepts. A logistic function used this way has come to be called a "risk function." With the use of suitable risk factors, one can identify highly vulnerable persons who would otherwise be missed by arbitrary categorical assessment and can estimate the magnitude of their risk over a wide range for each of the major cardiovascular diseases.

Among the various risk factors, an efficient set has been identified that, when synthesized into a risk function score, will select persons who are at high risk of coronary heart disease, atherothrombotic brain infarction, occlusive peripheral arterial disease and congestive heart failure. Using one set of coefficients for the



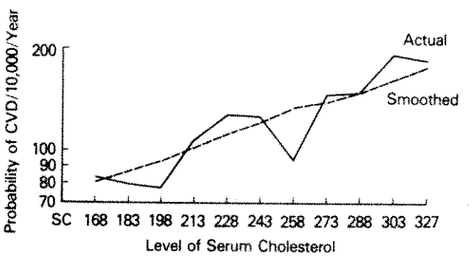


FIGURE 1 (left). Actual and smoothed probability of cardiovascular disease according to systolic blood pressure level: men and women aged 45 to 64 years, Framingham Study.

FIGURE 2 (right). Actual and smoothed probability of cardiovascular disease (CVD) according to serum cholesterol level: men and women aged 45 to 64 years, Framingham Study.

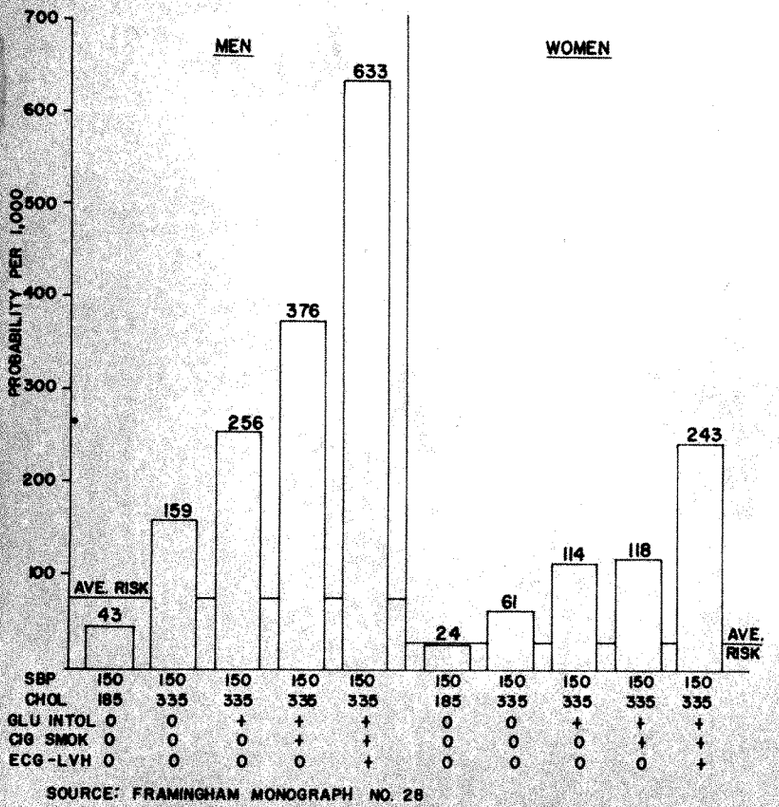


FIGURE 3. Risk of cardiovascular disease in 8 years at a systolic blood pressure of 150 mm Hg, according to intensity of other risk factors: Men and women aged 45 years, Framingham Study. AVE. = average; CHOL = serum cholesterol; CIG SMOK = cigarette smoking; ECG-LVH = electrocardiographic evidence of left ventricular hypertrophy; GLU INTOL = glucose intolerance; SBP = systolic blood pressure.

joint effect of these risk characteristics (including serum cholesterol, systolic blood pressure, glucose tolerance, electrocardiographic evidence of left ventricular hypertrophy and cigarette habit) it is possible to compute a risk function score. This can be done even though the variables used have a different impact on the incidence of each particular cardiovascular event.

With these variables—which can be obtained atraumatically in an unprepared patient, at modest cost using ordinary office procedures and simple laboratory tests—and knowing the person's age and sex one can predict cardiovascular events over a 20-fold range from the lowest to the highest decile of risk in both sexes. In this way one can identify the 10 percent of the general population who will have 22 percent of the coronary heart disease, 31 percent of the occlusive peripheral arterial disease, 43 percent of the brain infarction and 40 percent of the congestive heart failure.

Variation by Disease

Although the specified variables are appropriate for cardiovascular disease in general, their individual roles vary from one disease to the other, and by sex (Table II).[5] Whereas blood pressure is a major risk factor, it is distinctly more important as a precursor of brain infarction and heart failure than of coronary heart disease. Blood pressure is a minor factor, at best, in the background of persons with intermittent claudication, but cigarette smoking and glucose intolerance are major antecedents of this disease. Although cigarette smoking is an important factor in men for each of the four cardiovascular diseases cited, it tends to be a minor cardiovascular risk factor, overall, in women. The size of the standardized coefficients in Table II gives a reasonable approximation of the relative importance of each of the risk factors considered. (The data for serum cholesterol include an age constraint, since its role varies with age, being greatest for young adults and decreasing with age. A similar variation by age exists for cigarette smoking, but it is less critical to allow for it in the estimates. Age, as such, is omitted from Table II since it is not a reversible characteristic.)

Given this obvious heterogeneity of the regression coefficients among the various cardiovascular diseases it is fairly clear that it is less effective to use one risk function for all cardiovascular diseases than to use separate functions. However, it is obviously more practical to use a single function for cardiovascular screening provided the loss in efficiency in screening for persons at high risk for the specific diseases is not great.

Screening for persons at high risk: The simplest and perhaps most immediately relevant way of comparing the relative efficacy of a specific and general estimate of risk is in the context of screening for persons at high risk. Suppose a risk function is used to identify the 10 percent of the population at highest risk. How many cases would be identified as falling in this group with use of a specific function for the disease and how many with use of a general function for all cardiovascular disease?

To examine this question, the probability of each person at risk developing a specific disease was calculated and the population was then ranked from high to low according to this probability. To deemphasize the role of age, this ranking by level of risk was done separately for each 10 year age group and these age-specific populations were then ranked into deciles by level of risk. The actual number of events falling in each decile was counted. Ranking was done twice for each event, once using the coefficients for the specific event and once using the coefficients of total cardiovascular disease. As Table III shows, there is little to choose between these two methods of assignment; indeed, by chance, the general cardiovascular fit actually does *better* than the

TABLE II

Standardized Regression Coefficients for Incidence of Cardiovascular Disease for Specified Risk Factors: Men and Women Aged 35–64 Years (Framingham Study: 18 Year Follow-Up)

Risk Factors	Coronary Disease	Brain Infarction	Intermittent Claudication	Hypertensive Heart Failure*	Total Cardiovascular Disease
		Men			
Systolic blood pressure	0.245	0.587	0.205	0.542	0.326
Cigarette smoking	0.214	0.326	0.602	0.204	0.272
ECG-LVH	0.054	0.018	0.093	0.130	0.110
Glucose intolerance	0.051	0.158	0.221	0.287	0.133
Serum cholesterol†	0.441	0.412	0.424	0.099	0.403
		Women			
Systolic blood pressure	0.329	0.478	0.040	0.504	0.360
Cigarette smoking	−0.087	−0.005	0.209	0.392	0.019
ECG-LVH	0.068	0.074	0.158	0.093	0.083
Glucose intolerance	0.102	0.064	0.275	0.196	0.124
Serum cholesterol†	0.391	0.574	0.207	0.062	0.301

* Congestive heart failure in the absence of coronary or rheumatic heart disease.
† Regression coefficients for cholesterol at age 45.
‡ECG-LVH = electrocardiographic evidence of left ventricular hypertrophy.

specific fit for atherothrombotic brain infarction although this finding should not be taken too literally.

It should be emphasized that this table is comparing a rank ordering of persons from low to high risk, not an assessment of the actual probability that the disease will occur. Any reasonable function will put a person at greater risk of having, say, atherothrombotic brain infarction if his blood pressure is higher than if it is lower. A multivariate risk function, of course, may assign a somewhat higher or lower rank to persons with a given constellation of characteristics depending on the weights (coefficients) used, but rank is not especially sensitive to variation in the coefficients.

It may be argued that in some instances the apparent difference in coefficients among the specific cardiovascular diseases may be due more to random variation because of the small number of cardiovascular events available for estimation than to substantive differences. In those instances the coefficients for total cardiovascular disease should, in principle, be preferred to the coefficients estimated for the specific disease. However, this is an academic point in the absence of a method for deciding between the two sets of coefficients in specific instances.

Using the logistic risk functions for each specific cardiovascular cause one can define a group of people with a high probability of having each of these diseases and a group with a very low probability. Detailed tables based on actual levels rather than on deciles have been published elsewhere[6] and may be referred to for a concrete notion of "high" and "low" risk in each specific case. However, it is clear that groups at risks substantially higher and substantially lower than average can be defined by the risk function, although it is equally clear that a person at "high" risk is far from certain to have the disease and a person at "low" risk has no guaranteed immunity.

Discussion

Uses of the risk function: Although the pathogenesis differs from one cardiovascular disease to another, there is apparently a sufficiently large common process to warrant considering as a unit the incidence of cardiovascular disease in adults. This article discusses the properties of a general cardiovascular risk function on that assumption.

TABLE III

Number of Cases in Upper Decile of Risk According to Specific and General Cardiovascular Risk Profile

	Specific	General
Men		
Coronary heart disease (298)	62	61
Brain infarction (36)	11	14
Intermittent claudication (63)	20	20
Hypertensive heart failure* (31)	12	10
Women		
Coronary heart disease (198)	40	39
Brain infarction (44)	14	14
Intermittent claudication (41)	12	13
Hypertensive heart failure* (37)	16	13

*Congestive heart failure in the absence of coronary or rheumatic heart disease.

Figures in parentheses indicate total number of cases.

TABLE IV

Coefficients for Calculating Risk of Cardiovascular Disease

Variable	Coefficient	
	Men	Women
Age (years)	0.3743307	0.2665693
Age X age	−0.0021165	−0.0012655
Serum cholesterol (mg/ml)	0.0258102	0.0160593
Systolic blood pressure (mm Hg)	0.0156953	0.0144265
Cigarette smoking*	0.5583013	0.0395348
LVH by ECG*	1.0529656	0.8745090
Glucose intolerance*	0.6020336	0.6821258
Cholesterol X age	−0.0003619	−0.0002157
Intercept	−19.7709560	−16.4598427

* Yes = 1, no = 0 (for definitions see Shurtleff et al.[2]).

To obtain the probability that cardiovascular disease will occur in 8 years to a man or woman initially free of cardiovascular disease multiply the value of the characteristic in the units specified by the coefficient for the variable, sum these products and add the intercept. This provides the coefficient (C) to calculate the probability, $P = 1/(1 + e^{-C})$.

ECG = electrocardiogram; LVH = left ventricular hypertrophy.

TABLE V

Incidence of Cardiovascular Disease per 1,000 in 8 Years According to Decile of Cardiovascular Risk

	Men			Women		
Decile	45–54 Years	55–64 Years	65–74 Years	45–54 Years	55–64 Years	65–74 Years
1	51	102	128	21	62	144
2	65	121	146	26	74	128
3	77	140	173	31	85	144
4	89	157	184	36	95	160
5	104	175	204	42	106	173
6	120	197	224	48	117	190
7	141	221	252	56	131	211
8	168	256	296	66	152	234
9	214	316	387	87	191	294

TABLE VI

Probability by Age and Sex of Having Cardiovascular Disease in 8 Years (incidence per 1,000)

Age (yr)	Men	Women
35	18	5
40	41	12
45	75	25
50	115	48
55	159	80
60	193	119
65	212	160
70	229	199

There is another sense in which this is true and that is that one cardiovascular disease tends to lead to another. A person with coronary heart disease is substantially more likely to have a stroke than a person free of coronary heart disease.[7] Even nonspecific cardiac pathologic findings, such as heart enlargement on X-ray examination or electrocardiographic evidence of left ventricular hypertrophy, are precursive to a distinct excess in the incidence of stroke.[2,8]

By the same token, the risk function appropriate for estimating the 8 year risk of cardiovascular disease in persons free at the outset of any cardiovascular disease—the function presented in this paper—is no longer appropriate once a cardiovascular disease develops. What is more, the function only gives the probability of the first episode of a cardiovascular disease. Once a person has passed the acute phase of any cardiovascular disease the probability of recurrence is greater than the probability of the initial episode.

Clinical application: Although the utility of many of the proposed prophylactic measures for reducing the risk of cardiovascular disease still requires validation, there is an increasing level of belief in their efficacy and an increasing range of clinical intervention. Such programs require a rational method for identifying persons at high risk so as to focus attention on them and to avoid needlessly alarming persons at lower risk, because of a single stigma. By the same token, it is important not to provide false reassurance to persons with multiple marginal risk factors who may be at a much greater than average risk. The risk function, whether used as such or translated into a set of tables, is an effective instrument for avoiding both pitfalls and for assisting in the search for and care of persons at high risk of cardiovascular disease.

APPENDIX

The General Cardiovascular Risk Function

Table IV provides the coefficients necessary to calculate the probability that cardiovascular disease will occur in 8 years in persons initially free of such disease.

These probabilities are tabulated in Reference 5, and persons at high risk (say two or three times the average) can be determined from those tables. If probabilities are calculated directly, using the constants in the previous tables, two supplementary tables may be of help. One (Table V) shows the highest probability in each decile of cardiovascular risk. The other (Table VI) shows by age and sex the probability of an average person's having cardiovascular disease within 8 years.

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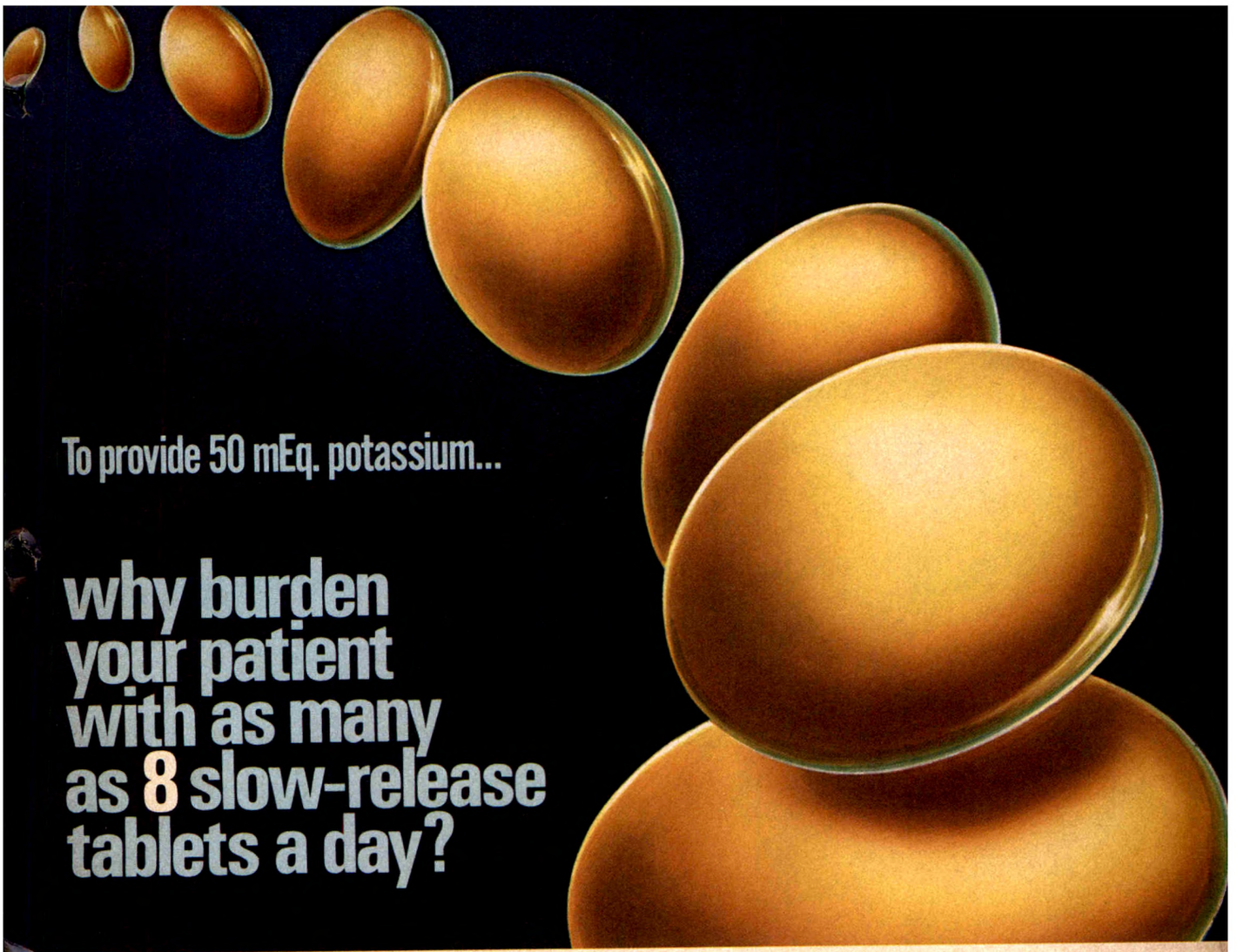

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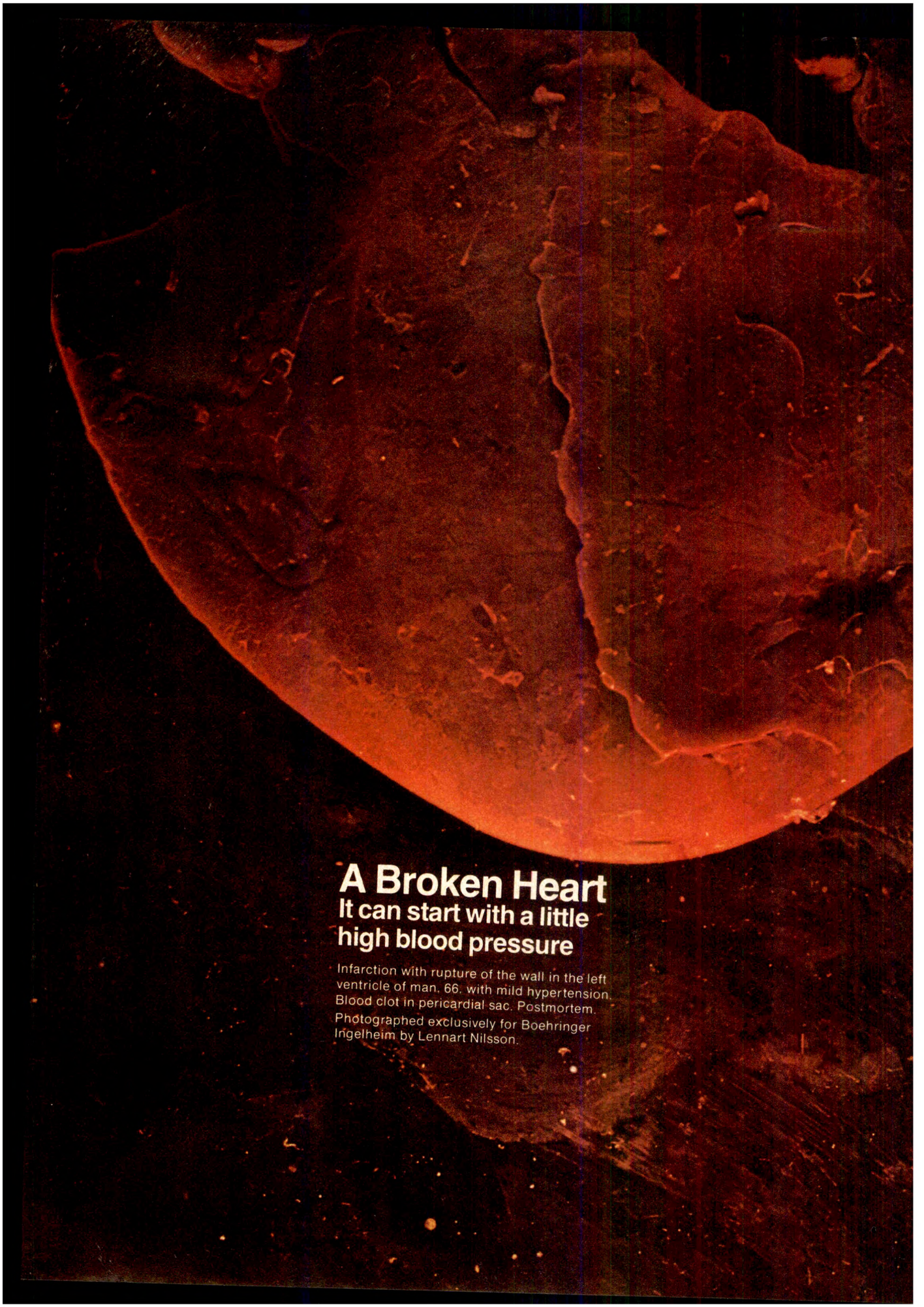
Warnings and Precautions: Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be administered with caution, and dosages adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal kidney function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Frequent checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also be directed toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients and such patients should be monitored by ECG for cardiac irregularities. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, **patients should be carefully directed to dissolve each dose completely in the stated amount of water.**

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts.

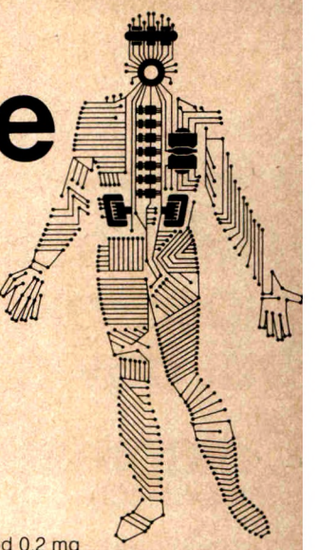
Dosage and Administration: Adults: 1 tablet (25 mEq. potassium) completely dissolved in **3 to 4 ounces of cold or ice water,** 2 to 4 times daily, depending upon the requirements of the patient. The normal adult daily requirement is approximately 50 mEq. of elemental potassium. NOTE: **It is suggested that this product be taken with meals and sipped slowly over a 5-10 minute period.**

How Supplied: K-Lyte effervescent tablets (orange or lime flavors) cartons of 30 and 250.

Mead Johnson LABORATORIES


A Broken Heart
It can start with a little high blood pressure
Infarction with rupture of the wall in the left ventricle of man. 66. with mild hypertension. Blood clot in pericardial sac. Postmortem.
Photographed exclusively for Boehringer Ingelheim by Lennart Nilsson.

Reach for normal blood pressure



In mild to moderate hypertension

Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl)

Catapres can make a diuretic look good.

When more than a diuretic is needed, adding Catapres usually lowers blood pressure more.[1]

You can add Catapres to Catapres to get pressure down near normal.

Wide therapeutic dosage range—0.2 mg to 2.4 mg* daily. Catapres may be all you need to reach near-normal levels.

*Doses as high as this have rarely been employed.

Catapres usually doesn't add a lot of problems.

The most common side effects—dry mouth, drowsiness, sedation—generally tend to diminish with time. When stopping Catapres, reduce dosage gradually over two to four days to avoid a possible rapid rise in pressure.

Please see next page of advertisement for
a brief summary of the prescribing information including
precautions, warnings, and adverse reactions.

Hypertension through the lens of Lennart Nilsson. The photographic genius of Lennart Nilsson has revealed extraordinary details of the human organism. Now, Boehringer Ingelheim has commissioned an exclusive series of photographs by Nilsson depicting hypertensive damage. This series, presented in the interest of continuing medical education, vividly records the progression of an insidious disease.

In mild to moderate hypertension

The Catapres Potential: blood pressure not just down, but down near normal

Catapres® Tablets of 0.1 and 0.2 mg (clonidine HCl)

Start with Catapres when a diuretic is wrong for your patient

Add Catapres when a diuretic alone doesn't let you reach near-normal pressure

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

Under license from Boehringer Ingelheim GmbH

Reference: 1. Data on file at Boehringer Ingelheim Ltd.

Boehringer Ingelheim Ltd.
Elmsford, New York 10523

Pedal-Mode Ergometry....

....a modular system for total stress control

Collins Pedal-Mode Ergometric System offers new dimensions in accuracy and reliability in the programming of physiologically paced ergometric tests.

Laboratory accuracy (± 2% of scale) and wide work load range (25 to 400 watts/sec.) are provided for the most demanding studies. In addition, a remote tachometer for subjects viewing and racing handlebars, seat and pedals are options which further enhance the Ergometer's functionability.

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Maintains patient's heart rate at a preselected level (with ± 3 bpm accuracy).

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Permits programming of the watt load for each of 10 steps. When used with the Cardiotachimetric Controller, the heart rate for each step is controlled and varied.

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Provides a graphic record of actual heart rate and work load.

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Provides cumulative digital readout of work units performed.

For complete brochure and prices write to Warren E. Collins, Inc., 220 Wood Road, Braintree, Mass. 02184.

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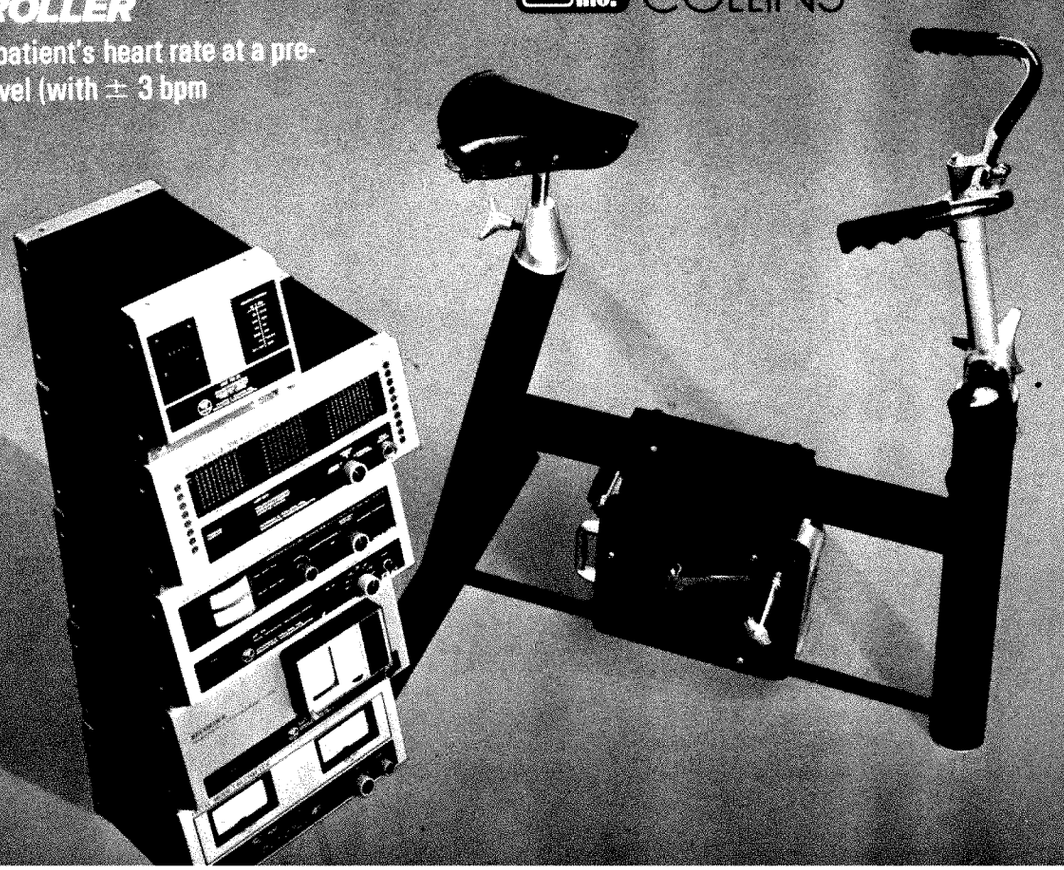
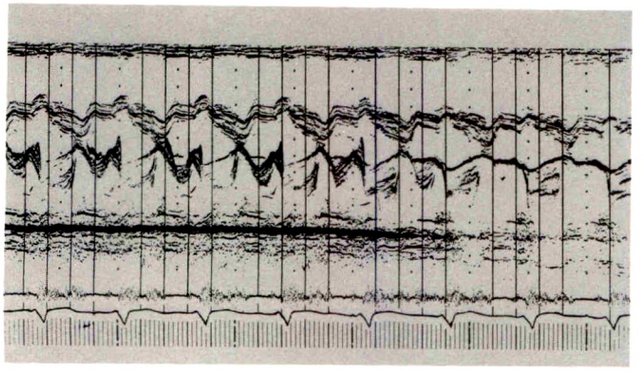
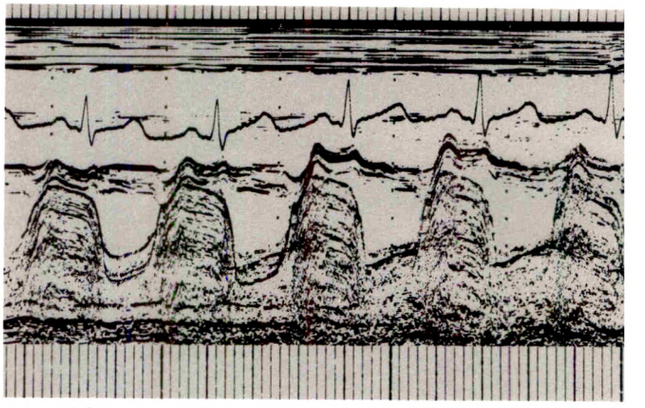


Echoview® 80C makes a big difference seem not so big.



Flail mitral valve leaflets secondary to bacterial endocarditis. Courtesy Dr. Raymond Gramiak, Strong Memorial Hospital, Rochester, New York.



Left atrial myxoma. Courtesy Dr. Roberta Williams, Children's Hospital Medical Center, Boston, Mass.

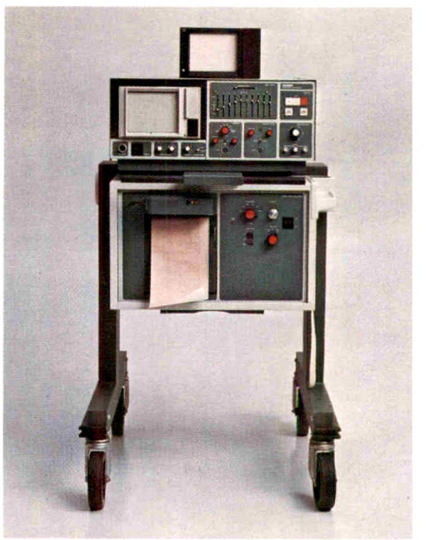
Picker's new Echoview System 80C with DSA enables you to diagnose many of their ailments accurately, easily. DSA™ (Depth Selective Amplification), developed exclusively by Picker, allows you to observe individual cardiac structures in context with all structures in the ultrasound beam.

Therefore, DSA means you focus on the diagnostically significant echoes. And to further improve your diagnosis, the capability to record physiological data together with the echogram is also provided.

Further, Picker's human engineering concept has resulted in the System 80C being a highly mobile, simple-to-operate and readily adaptable system for maximum clinical utilization.

System 80C is an example of Picker'synergy—the complete interfacing of systems and services for improved diagnostic visualization.

Contact your local Picker representative. Or write Picker Corporation, 12 Clintonville Road, Northford, CT 06472.



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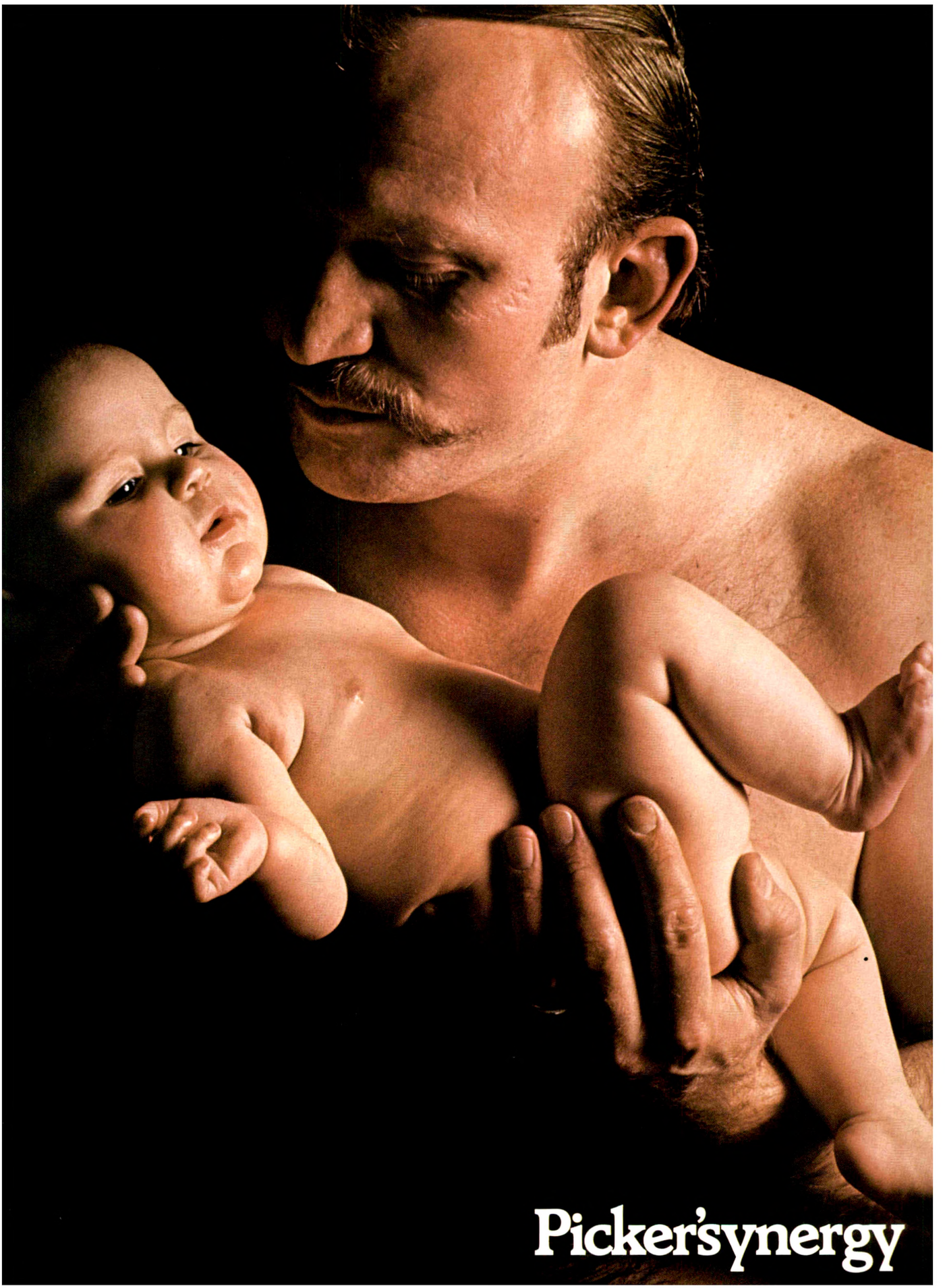
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Peritrate® SA Sustained Action

(pentaerythritol tetranitrate) 80mg

CAUTION: Federal law prohibits dispensing without prescription.

Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later. Tablets should not be chewed.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, double layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also in unit dose—package of 10 x 10 strips (N 0047-0004-11).

Additional Dosage Forms: Peritrate 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also in unit dose—package of 10 x 10 strips (N 0047-0001-11). Peritrate 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

Full information is available on request.

Defense against attack.

For over 22 years, Peritrate® has been considered by many physicians as one of the top defensive measures for patients with angina pectoris. In many patients Peritrate used prophylactically helps decrease the frequency and severity of angina attacks.* With minimal side effects.

Peritrate can also help reduce nitroglycerin requirements and, therefore, nitroglycerin side effects. Is it any wonder so many physicians continue to prefer Peritrate prophylaxis for their angina patients?

LONG-ACTING PROTECTION AGAINST ANGINA PAIN*

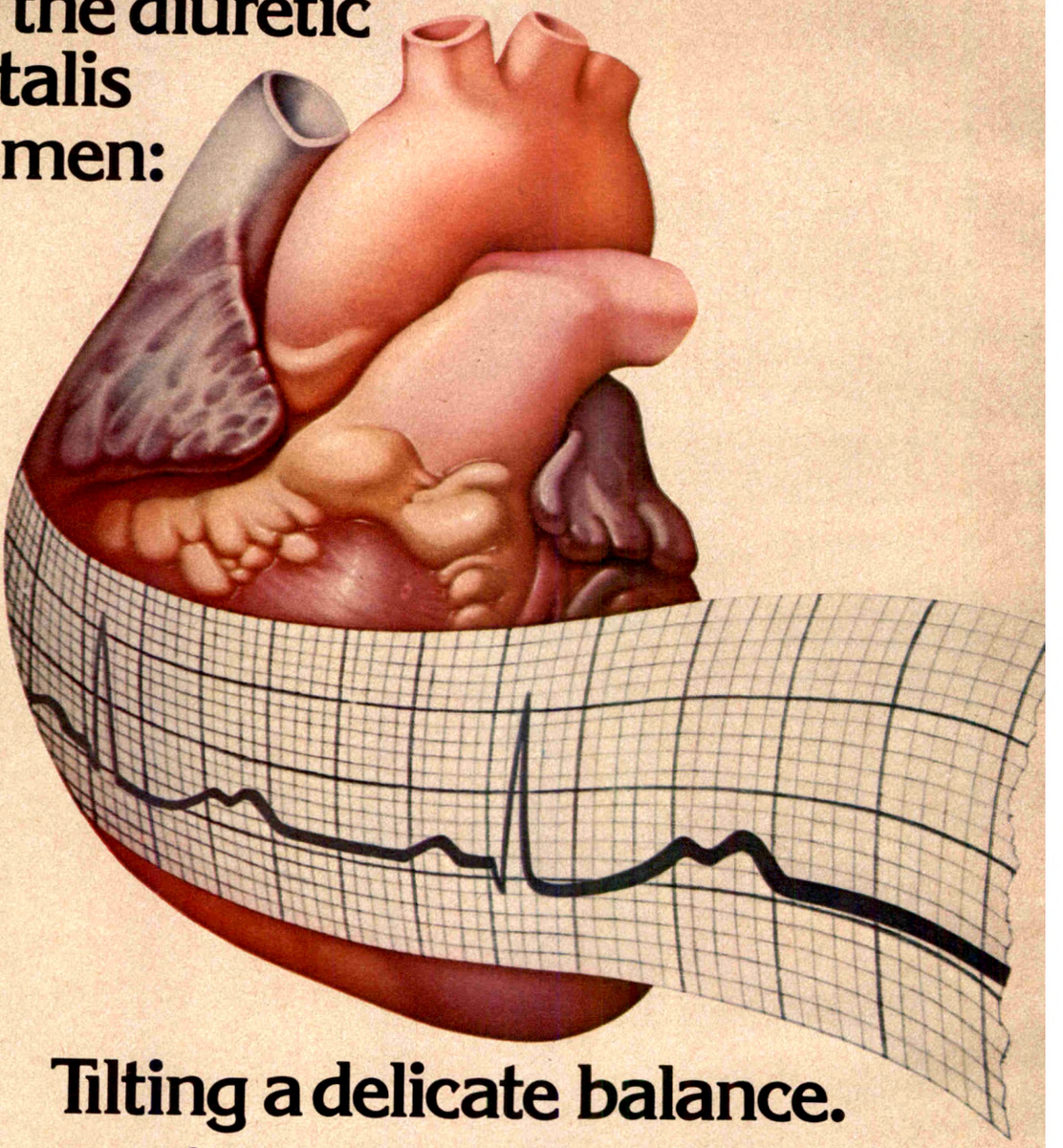
Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) 80 mg

Warner/Chilcott
Div. Warner-Lambert Company
Morris Plains, N.J. 07950
PE-GP-51

The Great Wall of China, an immense 1,400-mile-long man made barrier 20 to 30 feet high and 15 to 20 feet thick, helped defend China from the attack of Mongol hordes for more than 2,000 years.

*The drug has been evaluated as possibly effective for this indication.
See brief summary.

Hypokalemia and the diuretic digitalis regimen:



Tilting a delicate balance.

Certain diuretics such as thiazides, furosemide, and ethacrynic acid may remove potassium and the resulting potassium deficit can rapidly trigger arrhythmias in the digitalized patient. Of course, potassium supplements should not be administered with any potassium-sparing diuretics such as spironolactone and triamterene.

NOW
Kaon-CL 20%™
(potassium chloride)

Offers an economical, convenient therapeutic dose to correct hypokalemia or treat mild digitalis intoxication.

CONVENIENT, ECONOMICAL DOSAGE

■ One tablespoon (15 ml.) provides 40 mEq. each of potassium and chloride...nearly twice the potassium content of most single effervescent tablets or packets of powder.

■ Pleasant Cherry Flavor: One tablespoon (15 ml.) mixed with six fluid ounces of water or other liquid, few palatability problems are encountered. Kaon-CL 20% must be diluted before administration to avoid gastrointestinal irritation.

(See brief summary on following page for prescribing information.)

WARREN-TEED
PHARMACEUTICALS INCORPORATED
SUBSIDIARY OF ROHM AND HAAS COMPANY
COLUMBUS, OHIO 43215

Kaon-CL 20%™ (potassium chloride) Sugar-Free.

Description: Each 15 ml (tablespoonful) supplies 40 mEq each of potassium and chloride (as potassium chloride, 3 g) with saccharin and flavoring. Alcohol 5%.

Indications: Kaon-CL 20% is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. Kaon-CL 20% is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Warnings: Do not administer full strength. Kaon-CL 20% will cause gastrointestinal irritation if administered undiluted. For details regarding adequate dilution, see Dosage and Administration.

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation.

Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Dosage and Administration: Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.

One tablespoonful (15 ml) in six fluid ounces or more of water provides 40 mEq of potassium chloride.

One tablespoonful twice a day in six or more fluid ounces of water or other liquid provides 80 mEq potassium chloride.

Caution: Federal law prohibits dispensing without prescription.

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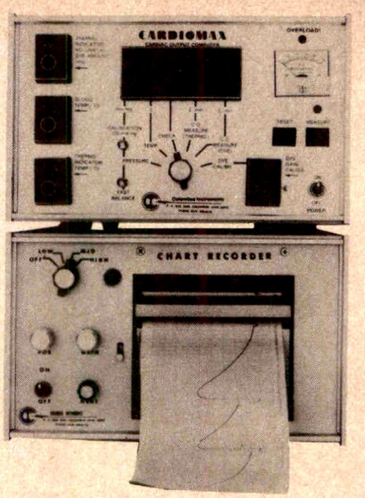

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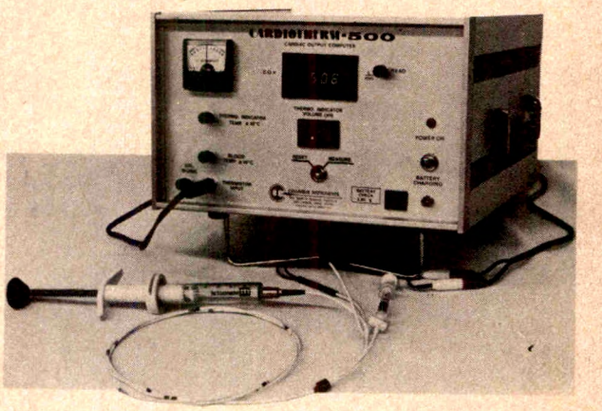
"CARDIOTHERM-500"



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*EXTRAPOLATES DILUTION CURVE.
*SMALL VOLUME ROOM TEMPERATURE INJECTIONS.
*PRICE: $3,300.00.

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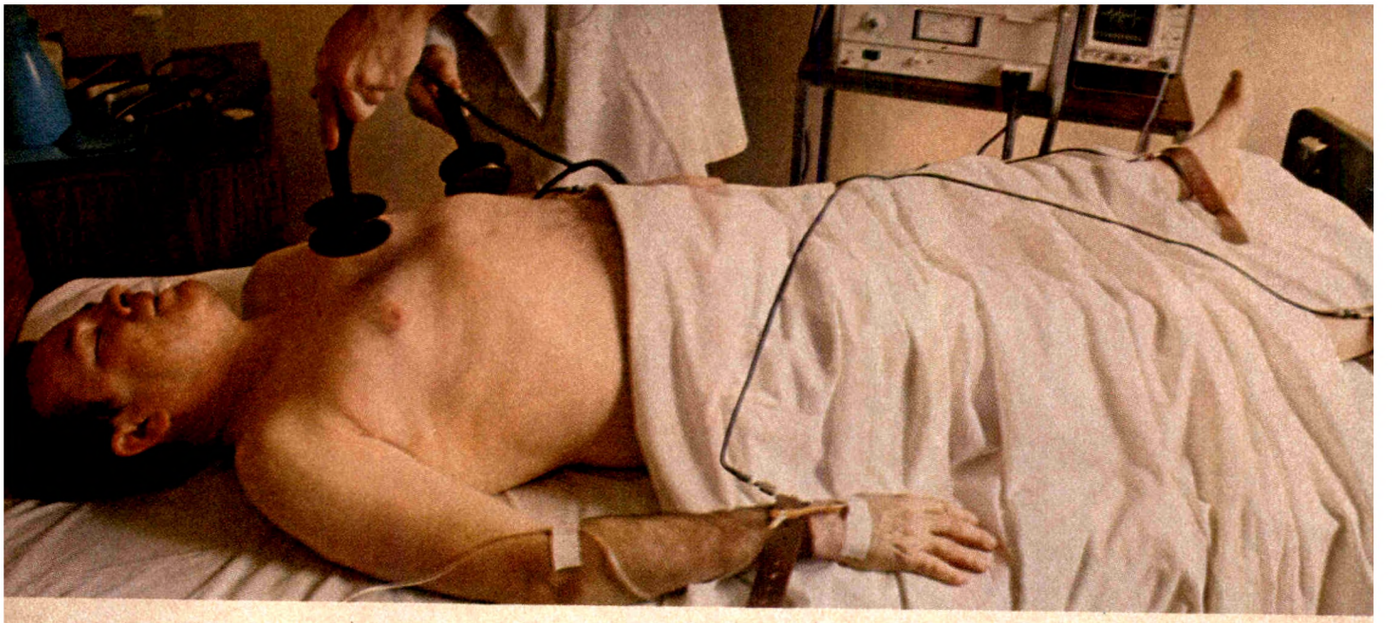


Less anxiety before elective cardioversion.

The patient is relaxed now, waiting quietly for you to begin. Although slightly drowsy, he appears well able to comply with instructions. And there's little trace left of the acute anxiety he was experiencing only a short while ago.

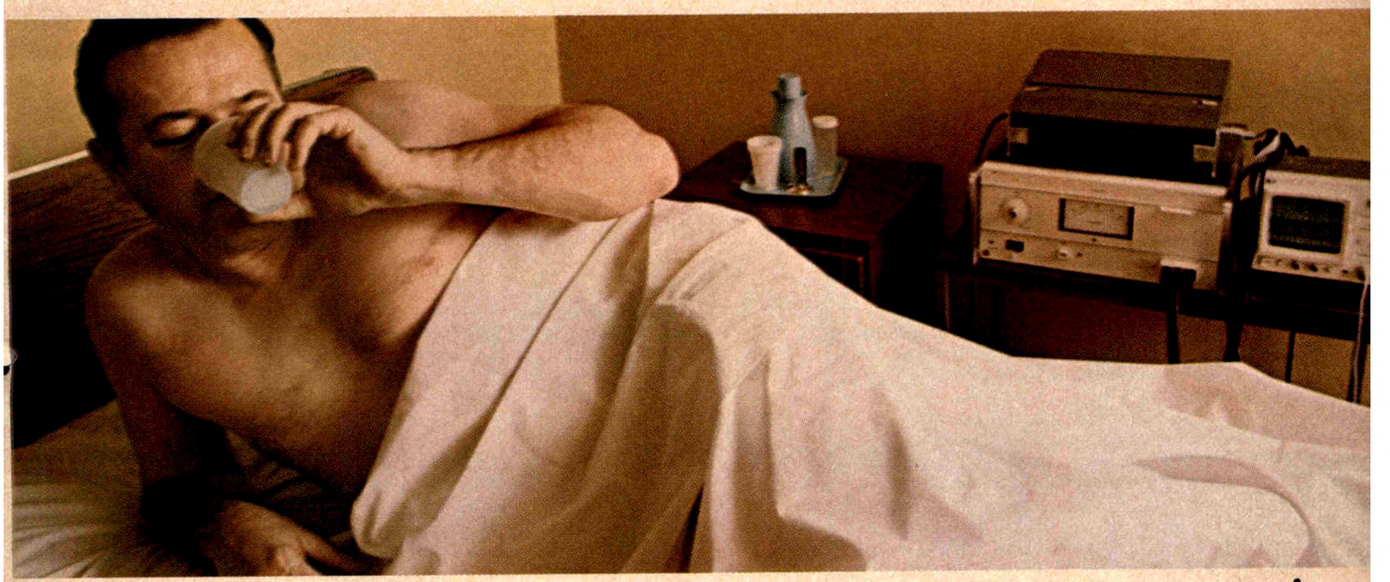
Injectable Valium® (diazepam) made the difference. Administered five to ten minutes before the procedure, Valium—5 to 15 mg injected I.V.—generally calms the overly tense, apprehensive patient and relieves much of his "anticipatory" emotional distress. In many cases, this eliminates the need for general anesthesia and O.R. scheduling.

In administering Injectable Valium, certain precautions must be taken. Valium must be injected slowly, taking at least one minute for each 5 mg (1 ml) given. To minimize local irritation, do not use small veins, such as those on the dorsum of hand or wrist. Extreme care should be taken to avoid intra-arterial administration or extravasation. And Valium should not be mixed or diluted with other drugs, solutions or fluids.

Although Injectable Valium (diazepam) seldom significantly alters vital signs, resuscitative facilities should be readily available. There have been occasional reports of apnea and/or cardiac arrest, particularly in elderly or very ill patients, or patients with limited pulmonary reserve.

Injectable Valium not only lessens the patient's anxiety but also can markedly diminish his memory of the countershock. This frequently contributes to a more emotionally comfortable rehabilitative period. Equally important—it helps reduce apprehension if a repeat procedure should become necessary.

Less recall afterwards.



Injectable Valium® (IV)
(diazepam)

for excessive anxiety prior to elective cardioversion

ROCHE

Before prescribing, please consult complete product information, a summary of which appears on the next page.

for excessive anxiety prior to elective cardioversion

Injectable Valium® (diazepam)

ready-to-use 2-ml Tel-E-Ject® (disposable syringes)
2-ml ampuls } 5mg/ml
10-ml vials }

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus and severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic and surgical procedures; cardioversion.

Contraindicated: In infants; in patients with known hypersensitivity to the drug; in acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *When used I.V., the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment. Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

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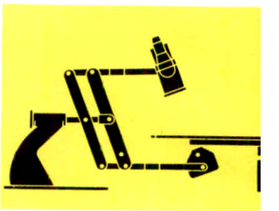

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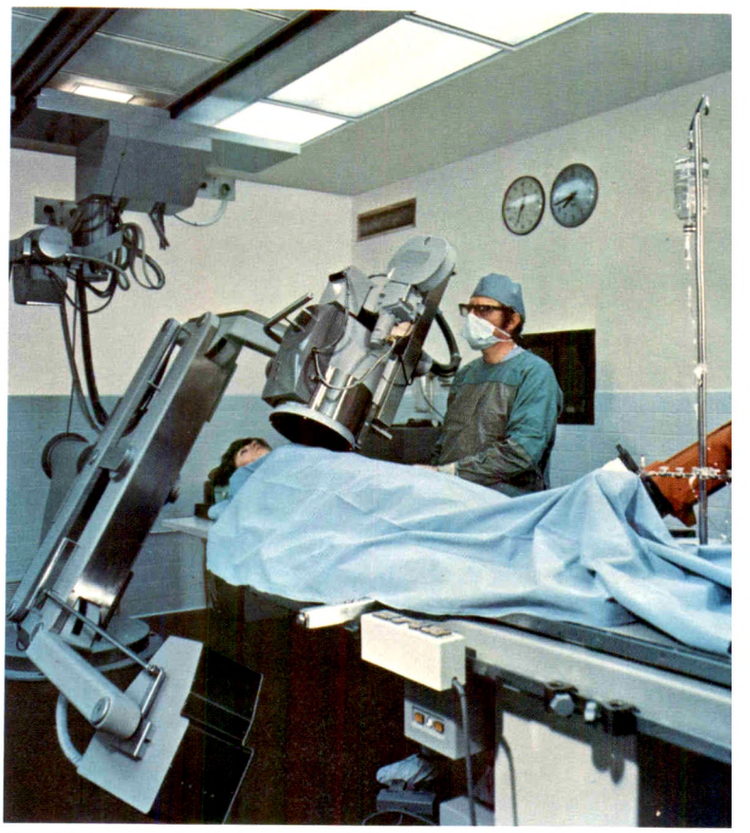

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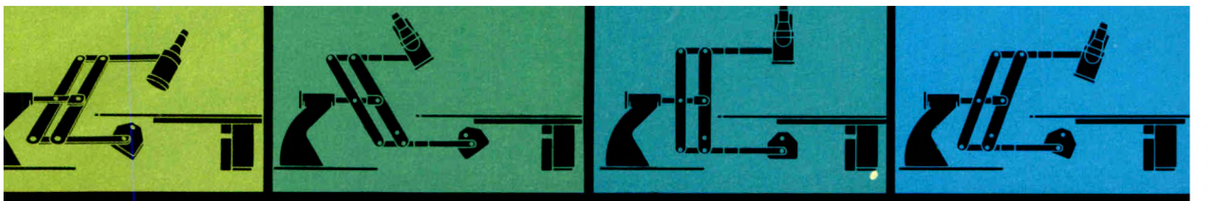

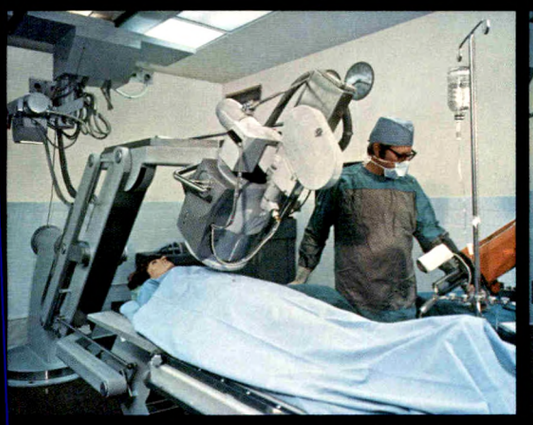

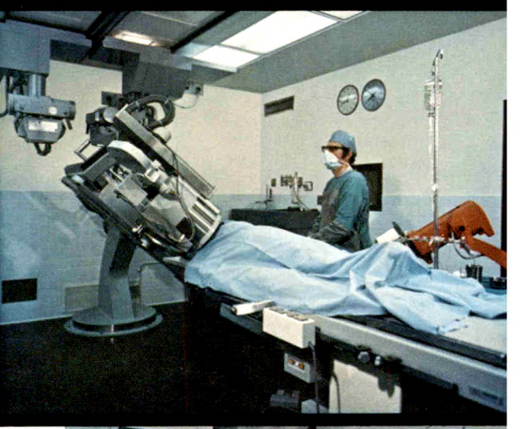

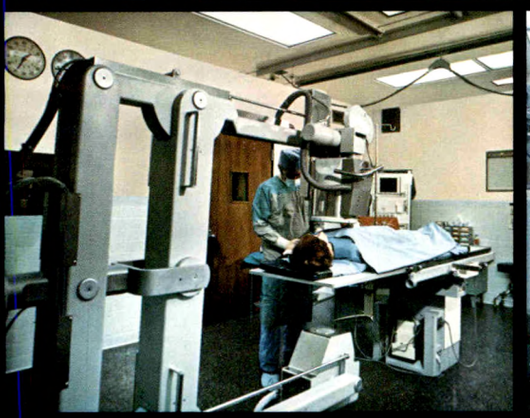

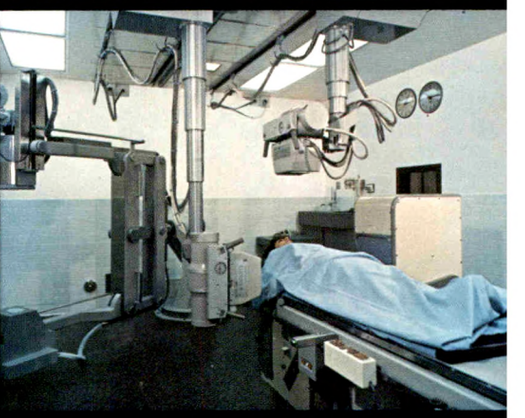

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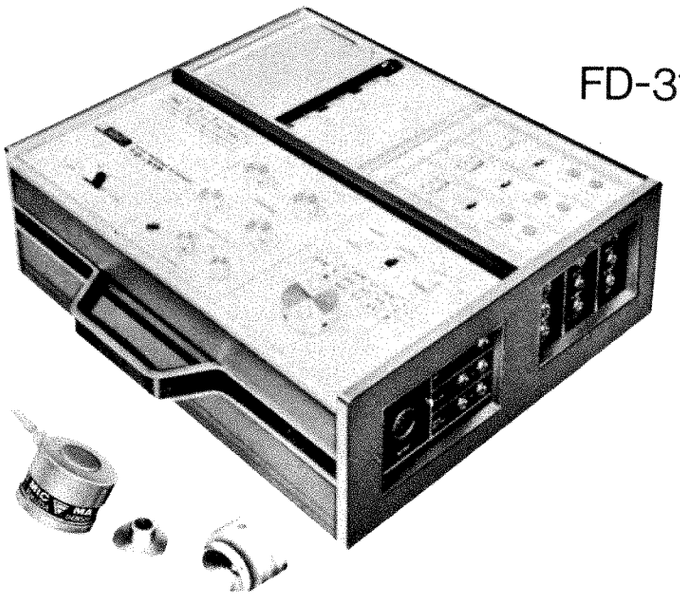

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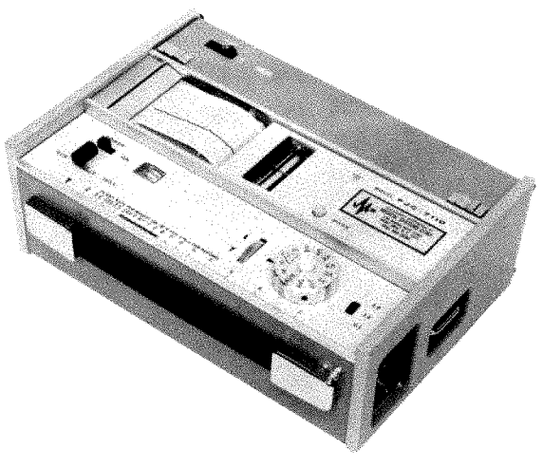

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Discrete Subvalvular Aortic Stenosis in Childhood

Study of 51 Patients

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Fifty-one children with discrete subvalvular aortic stenosis were studied between 1951 and 1974. The three anatomic types of obstruction found were the thin membranous type (43 cases), the fibromuscular collar type (5 cases) and the tunnel type (3 cases). The obstruction was usually severe, and the median left ventricular to aortic systolic pressure gradient was 90 mm Hg. Progressive obstruction with an increasing gradient was documented in 10 patients by serial cardiac catheterizations. Significant associated cardiac defects, present in 57 percent of patients, often masked the typical clinical and cardiac catheterization features of subaortic stenosis. The stenosis was often not discovered until after surgery for the associated defect.

Forty patients underwent surgical resection of the discrete subaortic obstruction. After surgery significant left ventricular to aortic pressure gradients can be found at postoperative cardiac catheterization. These gradients may reflect inadequate resection of the more complex discrete obstructions or represent proliferation and regrowth of the previously resected subvalvular fibrous tissue. The criteria for operability of discrete subaortic stenosis should be the angiographic demonstration of a discrete subvalvular diaphragm and the presence of a resting left ventricular to aortic systolic pressure gradient of 40 mm Hg or more.

Discrete subvalvular aortic stenosis constitutes 8 to 20 percent of all forms of left ventricular outflow obstruction reported in several large series.[1–4] Three types of discrete subvalvular aortic stenosis, as differentiated from idiopathic muscular subaortic stenosis, can be described. In the membranous type a thin fibrous diaphragm encircles the left ventricular outflow tract and is located a few millimeters to 2 to 3 cm below the valve.[5,6] This membrane may have attachments to the anterior leaflet of the mitral valve and is usually not more than a few millimeters thick. In the second type, a somewhat thicker fibromuscular obstruction can have a muscular base and form a collarlike outflow tract obstruction. In the most severe obstruction from the standpoint of surgical correction a fibromuscular tunnel narrows the left ventricular outflow tract for several centimeters.[7]

The obstruction is usually severe,[1,3,4,7–11] and a left ventricular to aortic peak systolic gradient of more than 60 mm Hg is common. Aortic regurgitation of various degrees is often associated, and may result from damage to the valve leaflets by the jet flow of blood through the stenotic subvalvular orifice. Some investigators[7,8,11] believe that early surgical intervention may prevent this damage to the aortic valve cusps.

This report reviews the clinical, hemodynamic and angiographic spectrum of discrete subvalvular aortic stenosis in childhood and discusses two important features not previously emphasized: (1) the masking of the typical clinical and cardiac catheterization findings by the presence of significant associated cardiac defects, and (2) the progressive nature of the left ventricular outflow obstruction in many patients. The angiographic findings, diagnosis and surgical results are emphasized.

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Methods

Case material: Fifty-one patients with discrete subvalvular aortic stenosis were seen at The Children's Memorial Hospital in Chicago from 1951 to 1974 (Table I). Their ages when first seen ranged from 18 days to 14 years (median 3 years). All the patients underwent cardiac catheterization, and all but one had left ventricular pressure measurements and angiography. Forty children had surgical resection of the subaortic obstruction. Eleven patients are dead, and postmortem examination was performed in 10 children, in 6 at The Children's Memorial Hospital and in 4 at other institutions (Table II).

Hemodynamic studies: Right and left heart catheterization was performed in 43 patients, right heart catheterization alone in 1 patient, and left heart study alone in 7 patients. The patients were sedated with a mixture of meperidine, promethazine and chlorpromazine. The left ventricle was entered in a retrograde manner in most cases, with a pullback pressure recording made from the apex of the left ventricle to the ascending aorta.

Surgical procedure: The patients were operated on over a period of 17 years by several surgeons, and the techniques varied. Before 1969 pressures in the ventricle and aorta were not routinely measured in the operating room. After 1969 the surgical technique was standardized, and all patients had left ventricular and aortic pressures measured at the termination of cardiopulmonary bypass.

The patients were all operated on utilizing cardiopulmonary bypass with a bubble oxygenator (Temptrol) primed with various proportions of 5 percent dextrose, Ringer's lactate solution and whole blood. Mild hypothermia of 30° C was used with local cooling of the heart with chilled Ringer's lactate solution. The incision was an oblique aortotomy with extension into the noncoronary aortic cusp.

The valves were retracted and the fibrous portion of the obstruction excised with care not to injure the aortic leaflet of the mitral valve. When excision of a muscular component was required, the incision was limited to an area under the right coronary cusp to avoid damage to conduction tissue.

Results

Clinical (Table I)

There were 36 boys and 15 girls in the entire group (male/female ratio 2.5:1). Two patients had a close family member with congenital heart disease. One had a brother with severe isolated infundibular pulmonary stenosis. The other patient had an identical twin with the same complex of defects,[12] consisting of severe aortic coarctation or interruption of the aortic arch, large ventricular septal defect and subaortic stenosis.

Auscultation: Most of the patients were initially referred because of a heart murmur, often diagnosed as a small ventricular defect or even considered functional. All patients had a systolic murmur, usually maximal at the mid-left sternal border with radiation to the base.

Aortic insufficiency was found in 28 patients (55 percent), 22 with an audible murmur and 6 without a recorded audible murmur but with angiographically confirmed mild aortic regurgitation. Twenty-three patients had mild insufficiency, as judged clinically and angiographically. Two had moderate and three had

TABLE I

Clinical Summary of 51 Cases of Discrete Subvalvular Aortic Stenosis

Patients (no.)	51
Male/female ratio	2.5:1 (36/15)
Age first contact	18 days to 14 years (median 3 years)
Patients with symptoms (no.)	22
Congestive heart failure	7
Dyspnea on exertion	9
Syncope/faintness	5
Chest pain	6
Sudden death	1 (2%)
Death secondary to complications	2 (4%)
Aortic insufficiency	28
Left ventricular-aortic resting systolic gradient (mm Hg)	20–160 (median 90)

TABLE II

Mortality Data (11 Cases)

Case no.	Diagnosis	Age at Death (yr)	Remarks
1	Fibromuscular collar + AS	2 11/12	Acute CHF 20 months after aortic valvotomy
2	Membranous obstruction	2 7/12	1 day after resection of membranous obstruction
3	Fibromuscular collar	14 2/12	Diabetes mellitus, CHB intraoperatively, resection of residual fibromuscular collar; died 1 day postoperatively with low cardiac output
4	Fibromuscular collar + muscular obstruction	15 5/12	Acute bacterial endocarditis, destruction of aortic valve
5	Membranous obstruction + ASD + VSD + supravalvular MS	2 4/12	1 day after Blalock-Hanlon procedure and PA banding
6	Membranous obstruction + AS	8 10/12	CHF, 5 months after aortic valvotomy and resection of membranous obstruction
7	Membranous obstruction + coarctation of aorta + PDA + VSD	5 1/12	2 days after closure of VSD and takedown of PA banding
8	Membranous obstruction + AS + supravalvular AS + supravalvular MS	10 6/12	Day of operation, homograft replacement of aorta, valvotomy and resection of membranous obstruction
9	Membranous obstruction + VSD	12 3/12	6 days after closure of VSD, grade IV pulmonary vascular disease[15]
10	Fibromuscular collar + coarctation of aorta + VSD + PDA	2 3/12	Acute CHF at home. Resection of coarctation; PDA ligation and PA banding at age 6 weeks
11	Membranous obstruction	20	Complete heart block and iatrogenic VSD at resection of membranous obstruction at age 11 years. Pulmonary embolus 2 months after uneventful pregnancy

AS = aortic stenosis; ASD = atrial septal defect; CHB = complete heart block; CHF = congestive heart failure; MS = mitral stenosis; PA = pulmonary arterial; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

severe regurgitation, two requiring aortic valve replacement.

Symptoms: Seven of the 51 patients in our series first presented with signs of congestive heart failure and associated cardiac defects that were thought to be the cause of the heart failure. The subaortic stenosis was discovered in five of these patients only after the associated defect had been surgically corrected or palliated.

In all, 22 patients in the series had symptoms; in addition to the 7 children with congestive heart failure, 9 had dyspnea on exertion, 5 had syncope or faintness and 6 had chest pain. Sudden death occurred in three patients, although only one death was of the nature usually associated with severe aortic stenosis. A 20 year old woman with postoperative complete heart block died after a pulmonary embolus 2 months after an uneventful pregnancy (Case 11, Table II). A 15 year old boy died after aortic valve rupture as a result of acute bacterial endocarditis (Case 4, Table II). The third death occurred suddenly at home in a 2 year old child 1 month before scheduled surgery (Case 10, Table II).

Electrocardiography: The electrocardiograms were reviewed for signs of ventricular hypertrophy and serial changes (Table III). Three patients consistently displayed the Wolff-Parkinson-White pattern, and assessment of ventricular hypertrophy was not possible. One infant had isolated severe right ventricular hypertrophy, probably related to the associated lesions, which included supravalvular mitral stenosis, ventricular septal defect and atrial septal defect. Four patients repeatedly had normal electrocardiograms, in spite of a left ventricular to aortic peak systolic pressure gradient of 75, 85, 90 and 100 mm Hg, respectively.

Forty-three patients (84 percent) had left ventricular hypertrophy, and 12 of them demonstrated a pattern of left ventricular strain with deeply inverted T waves in the left precordial leads. In 17 patients electrocardiograms were normal initially but serial records demonstrated progression to left ventricular hypertrophy or strain, or both.

TABLE III

Electrocardiographic Findings in 51 Cases

	no.	
Left ventricular hypertrophy	43	
Initially normal		17
+ Left ventricular strain		12
+ Right ventricular hypertrophy		9
Normal	4	
Wolff-Parkinson-White pattern	3	
Isolated right ventricular hypertrophy	1	
Total	51	

Cardiac Catheterization

The left ventricular to aortic resting peak systolic pressure gradient was more than 50 mm Hg in 45 patients (88 percent). The gradients ranged from 20 to 160 mm Hg (median 90). This gradient was measured across the subvalvular region; in two of the three patients with associated valvular stenosis an additional gradient was measured across the aortic valve.

Ten children had serial cardiac catheterizations without intervening surgical resection of the subaortic obstruction (Fig. 1). The resting left ventricular to aortic peak systolic pressure gradient increased in all 10 patients, and in 5 of these the increase was noted only after surgery for an associated cardiac defect. Seventeen children had cardiac catheterization after surgical resection of the subvalvular obstruction (Fig. 2). All but one had a reduction of the peak systolic left ventricular to aortic pressure gradient, but only eight patients had a postoperative gradient of 35 mm Hg or less.

Angiocardiography: The angiocardiograms were analyzed for the detailed anatomic features of the

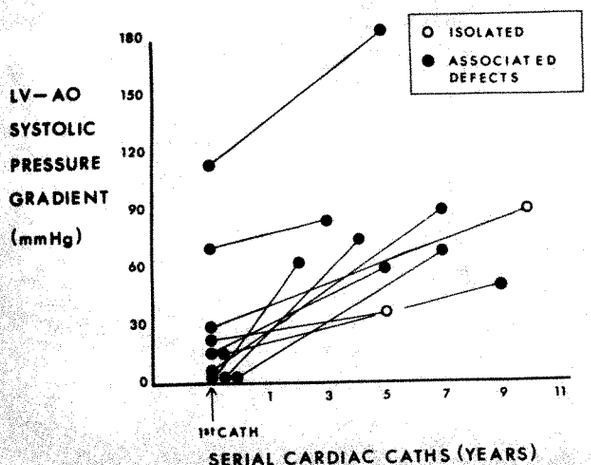

FIGURE 1. Increasing left ventricular to aortic pressure gradients documented by serial cardiac catheterization (CATH) studies. AO = aortic; LV = left ventricular.

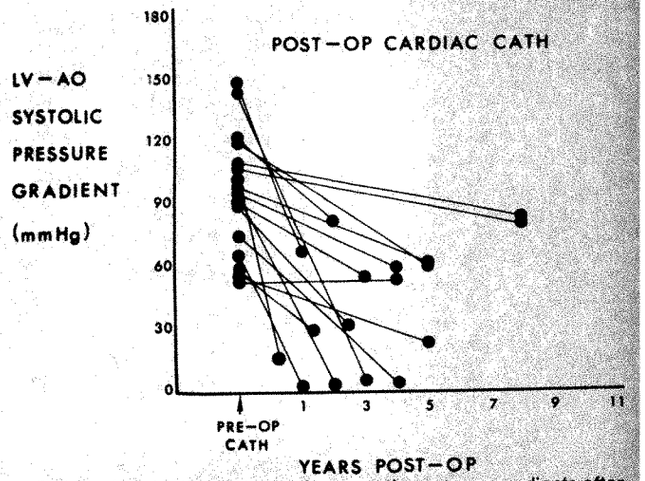

FIGURE 2. Residual left ventricular to aortic pressure gradients after surgical resection of subaortic obstruction, documented by cardiac catheterization. POST-OP = postoperative; PRE-OP = preoperative. Other abbreviations as in Figure 1.

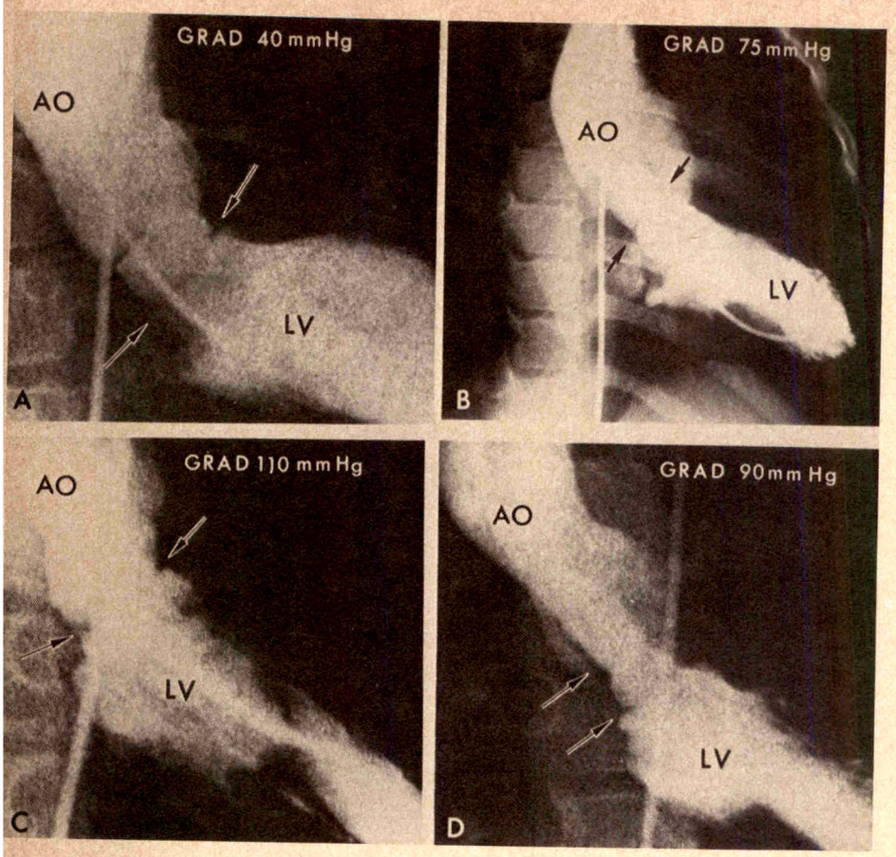

FIGURE 3. Angiographic demonstration of the anatomic types of discrete subvalvular aortic stenosis. **A** and **B,** thin membranous type; **C,** fibromuscular collar type; **D,** fibromuscular tunnel type. AO = aorta; GRAD = gradient; LV = left ventricle.

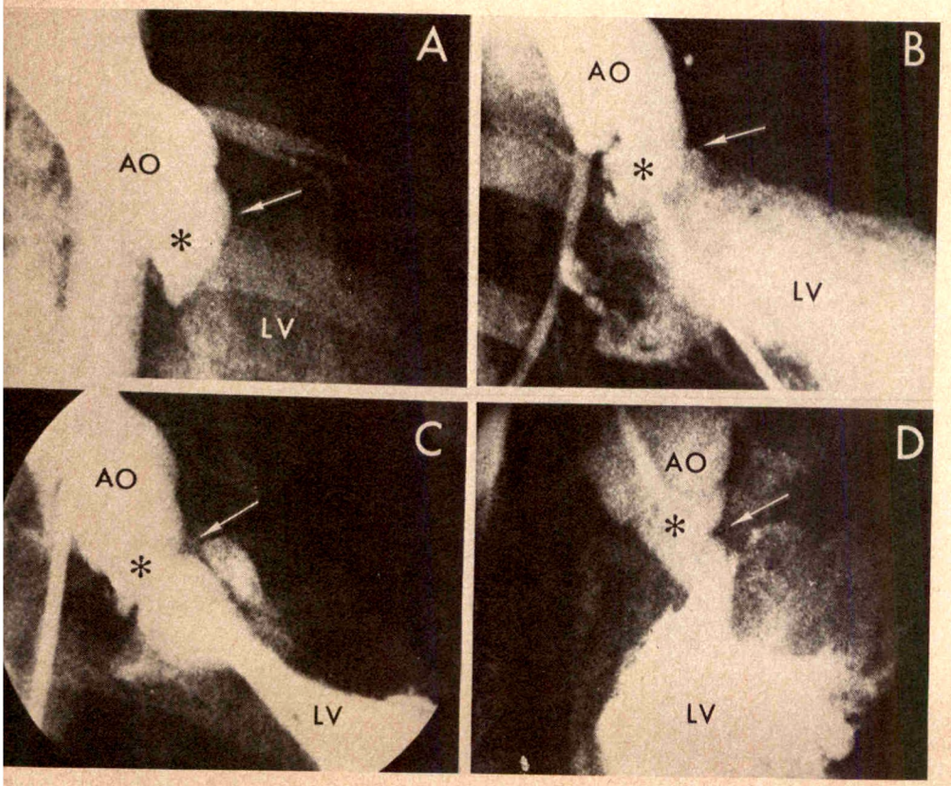

FIGURE 4. Angiographic features of discrete subvalvular aortic stenosis **(arrows). A** and **B,** aortogram and left ventriculogram in patient with associated aortic regurgitation. **Star** denotes the subvalvular chamber. **C** and **D,** left ventriculograms in two cases with associated muscular subaortic stenosis. Abbreviations as in Figure 3.

subaortic obstruction. A spectrum was found that included three basic types (Fig. 3). A thin fibrous diaphragm (Fig. 3, A and B) was present in 43 patients. A thicker diaphragm with a muscular base, having the angiographic appearance of a collar (Fig. 3C), was found in five patients. The difference between a somewhat thicker fibrous diaphragm and a fibromuscular collar was only one of degree, and the distinction was not clear-cut in every case. The third type was a tunnel-like narrowing of the left ventricular outflow tract (Fig. 3D) seen in three children.

The demonstration of aortic insufficiency often provided the best delineation of the discrete obstruction. With injection of contrast medium into the aorta (Fig. 4A), the subvalvular chamber was filled as a result of regurgitation of the medium with the lower border of the chamber consisting of the discrete diaphragm. A left ventricular injection in the same patient (Fig. 4B) also demonstrated the discrete diaphragm and the subaortic chamber.

Associated cardiac defects: Twenty-nine patients in the series (57 percent) had associated cardiac defects (Table IV). Sixteen (32 percent) had a documented left to right shunt. A ventricular septal defect was found in 11 children, 4 of whom also had other associated defects. Two patients had an aneurysm of the membranous septum and may have had a ventricular defect that underwent spontaneous closure. A shunt at the great vessel level only was seen in five patients, four with patent ductus arteriosus and one with aortic-pulmonary window.

There were 11 instances of additional left heart obstructing lesions. Three children had severe aortic valve stenosis and each underwent aortic valvotomy. One child had aortic valvotomy at age 2 years, but the subvalvular stenosis was not considered significant at the time of surgery and resection was not performed. She died of acute left ventricular failure 1 year postoperatively, and autopsy revealed severe subvalvular stenosis of the fibromuscular collar type and marked left ventricular hypertrophy (Fig. 5) (Case 1, Table II).

Six patients had coarctation of the aorta. Three had isolated coarctation, and three had an associated ventricular septal defect and patent ductus arteriosus. In two of these latter children, the left ventricular to aortic pressure gradient was absent until after they underwent surgical resection of the coarctation and patent ductus, and pulmonary arterial banding (Fig. 6).

Muscular subaortic stenosis was found in four children, and surgical resection was considered necessary in all of them. The angiographic appearance of the muscular subaortic stenosis was similar to that seen in idiopathic hypertrophic subaortic stenosis (Fig. 4, C and D). Echocardiograms obtained in two of them did not show systolic anterior movement of the mitral valve[13] or asymmetric septal hypertrophy.[14]

TABLE IV

Associated Cardiac Defects in 51 Cases

	no.
Left to right shunts	18
VSD (isolated)	7
VSD + coarctation of aorta + PDA	3
VSD + MS	1
PDA	4
Aortic-pulmonary window	1
Aneurysm of membranous septum	2
Obstructive lesions	11
Muscular subvalvular AS	4
AS	3
Coarctation of aorta	3
AS + supravalvular AS + MS	1
Total	29 (57%)

AS = aortic stenosis; MS = mitral stenosis; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

Surgery

Between 1959 and 1975, a total of 40 patients had surgical resection of the subaortic stenosis, and 3 had reoperation for severe residual obstruction. Thirty-two children had only subaortic resection at the primary operation, and eight had subaortic resection plus cor-

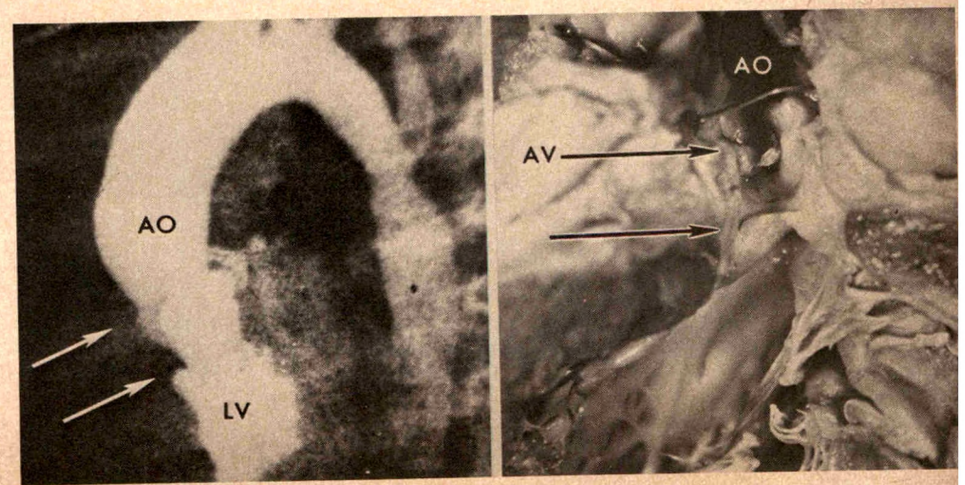

FIGURE 5. Valvular and subvalvular aortic stenosis. **Left,** preoperative left ventricular angiocardiogram. **Right,** postmortem findings. The **upper arrows** point to the stenotic aortic valve and the **lower arrows** point to the discrete subvalvular obstruction in both panels. AV = aortic valve. Other abbreviations as in Figure 3.

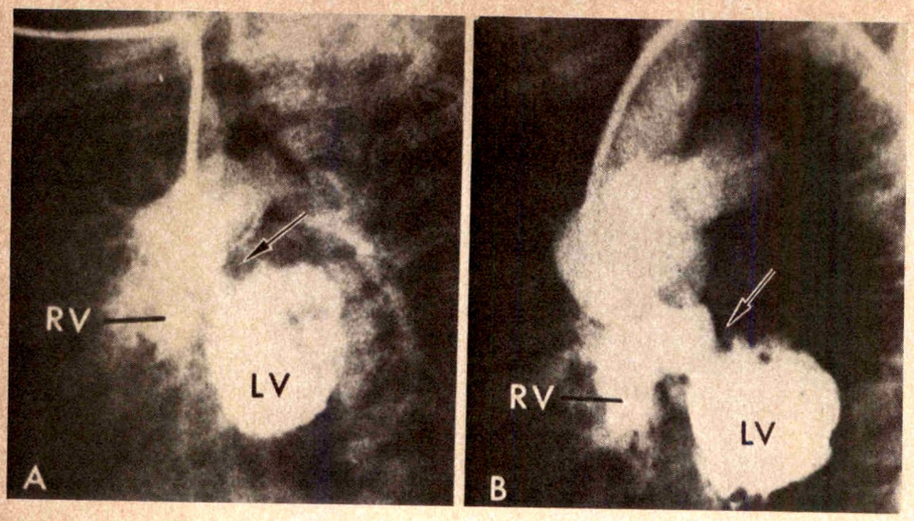

FIGURE 6. Discrete subvalvular aortic stenosis associated with coarctation of the aorta, ventricular septal defect and patent ductus arteriosus. **A,** initial cardiac catheterization at age 2 months. Left ventricular pressure is 110/8, aortic pressure 110/80 mm Hg. **B,** cardiac catheterization at age 7 years, postoperative resection of coarctation, ligation of patent ductus arteriosus and pulmonary arterial banding at age 3 1/2 months. Left ventricular pressure is 190/10, aortic pressure 110/60 mm Hg. LV = left ventricle; RV = right ventricle.

rection of an associated cardiac defect at the same operation. There were two operative deaths at the primary resection (Cases 2 and 8, Table II), an operative mortality of 5 percent; one death occurred after reoperation for residual stenosis (Case 3, Table II). There were 20 separate operations for associated cardiac defects, and there were three operative deaths (15 percent) (Cases 5, 6 and 9, Table II).

In four patients, permanent complete heart block developed at surgery. As mentioned, one of them died in the immediate postoperative period of a reoperation for residual stenosis (Case 3, Table II), and one died suddenly 7 years postoperatively from a pulmonary embolus (Case 11, Table II) 2 months after an uneventful pregnancy. One child was found to have a left ventricular-right atrial shunt after resection of the muscular base of a subaortic fibrous diaphragm, and one patient with complete heart block was found to have a small iatrogenic ventricular septal defect.

Discussion

Severity and Progression of Left Ventricular Obstruction

Discrete subvalvular aortic stenosis is often a severe form of left ventricular obstruction, and a left ventricular to aortic pressure gradient of more than 50 mm Hg was found in 88 percent of our study group. Forty-three patients (84 percent) manifested electrocardiographic evidence of left ventricular hypertrophy (Table III), and 20 percent had T wave inversion in the left precordial leads, demonstrating left ventricular strain.

Ten patients who underwent serial cardiac catheterizations without surgery for the subaortic stenosis had progressively increasing degrees of obstruction (Fig. 1). Five of the patients with associated defects had surgery for the associated defect in the interval between studies. Whether the progressive nature of the obstruction is due to proliferation of the fibrous tissue further narrowing the lumen or to the fixed size of the orifice relative to the growth of the patient is not known. Several patients whose data are shown in Figure 1 were underdeveloped physically at the time of the first cardiac catheterization, and manifested improved growth at the time of the second study. An accelerated growth spurt may be another factor in some of the apparent progression demonstrated. Progressive proliferation of fibromuscular tissue occurs in the left ventricular outflow tract of some patients with complete transposition of the great vessels, and results in a left ventricular outflow tract pressure gradient, but the mechanism of progression may be quite different in these two conditions.

TABLE V

Associated Defects in Patients With Subaortic Stenosis: Present and Previously Reported Series

Reference and Year	Total Patients (no.)	Patients With Associated Defects	
		no.	% of Series
Braunwald et al.[1] (1963)	20	5	25
McGoon et al.[3] (1969)	30	8	26
Reis et al.[7] (1971)	30	16	53
Shariatzadeh et al.[8] (1972)	20	2	10
Kelly et al.[9] (1972)	25	6	24
Champsaur et al.[10] (1973)	20	5	20
Blieden et al.[11] (1973)	34	12	35
Present series (1976)	51	29	57

Associated Defects

Associated cardiac defects (Table IV) were found in more than half of our patients (57 percent), an incidence greater than that reported in most other large series (Table V). Significantly, the diagnosis of subaortic stenosis was not suspected initially in 19 of the 29 children (65 percent) with these associated cardiac defects.

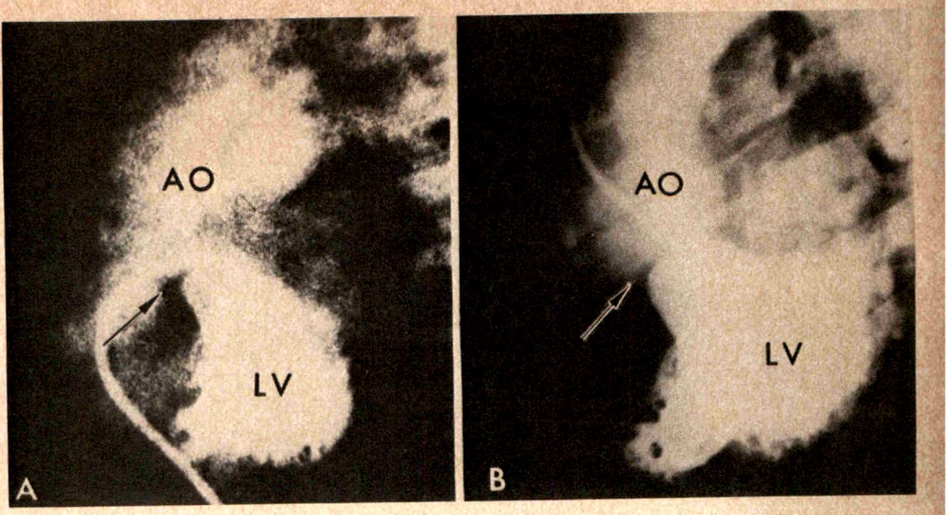

FIGURE 7. Discrete subvalvular aortic stenosis **(arrows)** and associated ventricular septal defect. **A,** initial cardiac catheterization at age 3 months; left ventricular pressure is 100/10, aortic pressure 95/50 mm Hg. The ventricular septal defect was surgically corrected at age 4 years. **B,** repeat cardiac catheterization at age 7 years; left ventricular pressure is 165/7, aortic pressure 90/60 mm Hg. AO = aorta; LV = left ventricle.

This finding was most common in the presence of a large left to right shunt. None of the other reported series of patients with this lesion mention the possibility of the associated defect masking the diagnosis of discrete subaortic stenosis.

Patent ductus or aortic-pulmonary window: In the five children with shunts at the great vessel level, the diagnosis of subaortic stenosis was not considered until a loud cardiac murmur became evident after the shunts were surgically closed. None of them had left heart studies preoperatively, but all had a left ventricular to aortic pressure gradient of 50 to 100 mm Hg at cardiac catheterization studies 1 to 7 years after surgical closure of the shunting lesion.

Ventricular septal defect: In three of the seven patients with an associated isolated ventricular septal defect, the diagnosis of subaortic stenosis was not apparent until cardiac catheterization was repeated after closure of the ventricular defect. Intraoperative pressure measurements in the aorta and left ventricle were not routinely performed after closure of the defect. One of these children (Fig. 7) had a preoperative study at age 22 months that revealed the ventricular septal defect but no significant left ventricular to aortic pressure gradient. However, later review revealed demonstration of a subaortic diaphragm in the angiocardiogram (Fig. 7A, arrow). The ventricular septal defect was closed surgically at age 4 years. Cardiac catheterization performed at age 7 years because of a persistent systolic murmur and left ventricular hypertrophy demonstrated a 75 mm Hg left ventricular to aortic gradient, and the angiogram more clearly demonstrated the constricting fixed subvalvular diaphragm (Fig. 7B, arrow).

Initial absence of pressure gradients also occurred in two patients with a combination of ventricular septal defect, coarctation of the aorta and patent ductus arteriosus (Fig. 6). As in the previous case, the preoperative study did not reveal significant pressure gradient. Again, retrospectively there is a suggestion in the angiogram of a subvalvular narrowing (Fig. 6A, arrow). Cardiac catheterization 6 1/2 years after surgical resection of the coarctation and pulmonary arterial banding revealed a left ventricular to aortic gradient of 80 mm Hg, and the angiocardiogram more clearly demonstrated the subaortic stenosis (Fig. 6B, arrow).

There are several possible explanations for these findings of obscured left ventricular outflow tract obstruction. One is that the subaortic stenosis was initially minimal but became progressively more severe over several years. Our study and others[4] have demonstrated that such progression can occur in some patients, even without associated cardiac defects. Another possibility is that a large ventricular septal defect proximal to the subaortic stenosis can, by decompressing the left ventricle, minimize the left ventricular outflow tract pressure gradient until the ventricular septal defect is closed. Only after the defect is closed will the pressure gradient be fully revealed.

Coarctation: In the presence of coarctation of the aorta and ventricular septal defect, the combination of severe congestive heart failure and distal aortic obstruction may be sufficient to minimize the subaortic gradient. After surgical resection of the coarctation and pulmonary arterial banding relieve the congestive heart failure, the left ventricular to aortic gradient becomes manifest.

Valvular aortic stenosis and muscular subaortic stenosis: The presence of valvular, supravalvular or muscular subvalvular aortic stenosis in association with discrete subaortic stenosis makes accurate diagnosis difficult. High quality left ventricular angiography is necessary to demonstrate the discrete subvalvular obstruction. If present, this should always be resected at the time of surgery for the other obstructing lesions. Failure to do so may have contributed to a preventable sudden death in our Case 1 (Fig. 5).

Criteria for Surgery

Because of the likelihood of progression of the left ventricular outflow tract obstruction in discrete sub-

aortic stenosis, it is unreasonable to use the same pressure gradient criteria for operation as those used in valvular aortic stenosis. The presence of a left ventricular to aortic pressure gradient of 40 mm Hg with isolated discrete subaortic stenosis is a reasonable criterion for surgical resection, since progression to much higher gradients is probable. The discovery of a discrete subaortic stenosis in association with other cardiac defects should prompt resection at the time of surgery for other defects, even if the gradient is less than that usually considered to represent significant left heart obstruction.

Since completion of this study we have seen three additional children with membranous subvalvular aortic stenosis associated with a large ventricular septal defect. Two patients had a left ventricular to aortic gradient of 10 and 20 mm Hg, respectively, and the third had no demonstrable gradient. All three had the subvalvular fibrous membrane resected at the time of closure of the defect, and its appaearance was the same as that found in patients with a significant gradient. We believe that if the membrane had not been resected at the time of closure of the defect it would have subsequently produced significant left heart obstruction.

Aortic regurgitation: Early surgical resection of a subaortic diaphragm may prevent damage to the aortic valve commonly associated with discrete subaortic stenosis. Thickening of the aortic valve cusps produced by the turbulence of blood flow through the stenosis is believed by some investigators[1,8,11] to lead to aortic regurgitation. Three patients in our study had severe aortic insufficiency, and two have had valve replacement. Valve replacement may be required in the future for other patients whose aortic regurgitation is now only moderately severe.

Persistence of Significant Obstruction After Surgery

Seventeen of the 40 patients who had surgical resection for the discrete subaortic stenosis had cardiac catheterization from 1 to 8 years postoperatively (Fig. 2). In nine of these patients, the residual left ventricular to aortic gradient was 50 mm Hg or greater, and three have had repeat surgical resection. The subvalvular stenosis was caused by more than just a thin diaphragm in five of these children. Three had associated muscular subaortic stenosis, one had a fibromuscular collar type of stenosis, and one had a tunnel type of obstruction.

All but two of these patients were operated on before 1969, and the techniques of surgery varied. Also, intraoperative post-pump pressures were not obtained, so we do not know whether the gradient found at postoperative cardiac catheterization represents obstruction not adequately resected at the initial surgery, or actual regrowth of the subvalvular tissue. In two patients post-pump gradients were measured, and in one an 18 mm Hg gradient increased to 50 mm Hg at a catheterization study performed 5 years postoperatively and in the other patient a 40 mm Hg post-pump gradient increased to 80 mm Hg 2 years after operation. Both of these patients had associated muscular stenosis.

Associated muscular aortic stenosis: Reis et al.[7] demonstrated a decrease in the muscular component of obstruction associated with discrete subaortic stenosis in several patients at serial postoperative cardiac catheterizations. In that series, however, some obstruction was found to persist as demonstrated by abnormal postextrasystolic beat responses. Three of the four patients in our study with associated muscular subaortic stenosis had cardiac catheterization after surgical resection of the discrete stenosis and myectomy. A residual gradient of 80, 60 and 80 mm Hg was noted 2, 5 and 8 years, respectively, after operation.

Causes of persisting obstruction: The surgeon may be reluctant to excise radically the obstructing tissues because of the possibility of damage to the mitral valve, production of complete heart block or the creation of ventricular septal defects. Iatrogenic ventricular defects occurred in two patients in our series.

Persistence or recurrence of significant subaortic stenosis after surgical resection has been reported by other investigators.[1,3,8–10,14] When the stenosis is due to a thin fibrous diaphragm, adequate surgical resection will generally result in permanent relief of the obstruction. When there is a thick muscular base of the diaphragm, or it has significant attachment to the mitral valve, relief of the stenosis can be less satisfactory. Attempts to relieve the tunnel type of subaortic stenosis have been generally poor.[3,7] It is also possible that in some patients the residual stenosis documented at postoperative cardiac catheterization is due to proliferation and regrowth of fibromuscular obstructive tissue.

Conclusions

Discrete subvalvular aortic stenosis can be a cause of severe left ventricular outflow obstruction, even in infants and young children. It can produce a progressive obstruction, and usually causes severe left ventricular hypertrophy. Associated cardiac defects occur in approximately half of the patients, and their presence can obscure the clinical and catheterization diagnosis of the subaortic stenosis.

Surgical resection of the discrete subvalvular obstructing tissue usually relieves the stenosis particularly when it is due to a thin fibrous diaphragm, but significant left ventricular aortic gradients have been found postoperatively. These postoperative pressure gradients may reflect inadequate surgical resection of the more complex discrete obstructions, or may represent proliferation of the previously resected subvalvular fibrous tissue. Serial cardiac catheterizations postoperatively in most patients with discrete subaortic stenosis are necessary to detect either residual obstruction or restenosis years after operation.

The criteria for operability for discrete subaortic stenosis should not be as stringent as for valvular aortic stenosis. The angiographic demonstration of a discrete subvalvular diaphragm and the presence of a left ventricular to aortic pressure gradient of 40 mm Hg or greater should prompt surgical resection of the lesion.

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Pulmonary Blood Flow Distribution in Transposition Of the Great Arteries

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Pulmonary blood flow distribution was studied by scintillation scanning of the lungs after the infusion of iodine-131–labeled macroaggregates of human albumin before and after the Mustard operation in 53 patients with transposition of the great arteries. The patients were classified as follows: Group I (24 infants with uncomplicated transposition of the great arteries); Group II (18 patients with transposition and ventricular septal defect); and Group III (11 patients with transposition, ventricular septal defect and pulmonary obstruction).

Before operation, 21 patients had a normal distribution of pulmonary blood flow, 10 had preferential flow to the right lung and 2 had preferential flow to the left lung. After operation, 19 had a normal pattern of pulmonary blood flow, 21 had preferential flow to the right lung and 3 had preferential flow to the left lung. The scanning studies have proved helpful in follow-up of patients to rule out recurrence of the shunt, pulmonary or systemic venous obstruction, development of pulmonary hypertension and occlusion of a palliative systemic-pulmonary shunt.

Unequal regional distribution of pulmonary blood flow associated with congenital heart disease has been reported,[1–3] but we know of no single large series intended to elucidate the distribution pattern of pulmonary blood flow in transposition of the great arteries. This study was initiated prospectively to evaluate this pattern before and after hemodynamic corrective surgery in children with transposition. Pulmonary blood flow distribution can now be determined accurately and reproducibly by scintillation scanning of the lung after infusion of iodine-131–labeled macroaggregates of human albumin.[4–6]

Material and Methods

Fifty-three patients with transposition of the great arteries were studied within a 3 year period. In 35 patients, pre- and postoperative scintillation lung scans were obtained; in 7 lung scans were obtained only preoperatively and in 11 only postoperatively. The age of the patients ranged from 4 weeks to 35 years. Thirty-nine were less than 2 years old; only 2 were more than 12 years old. In all patients complete correction of transposition of the great arteries was performed by the intraatrial baffle technique developed by Mustard in 1963. Forty-nine patients in this series were operated on under surface-induced deep hypothermia, limited cardiopulmonary bypass and circulatory arrest.[7] ^{131}I macroaggregates of serum albumin were given intravenously into a right arm vein in a dose of 3 to 4 μCi/kg body weight with the patient supine. The injections were not given while the child was crying, because the Valsalva maneuver may interfere with free passage of the dose from the vein into the thorax. A sedative and a waiting time after the needle insertion were enough to avoid this problem. Approximately 10 minutes after injection, anterior and posterior lung scans were performed with the Ohio Nuclear rectilinear scanner or scintiphotographs of both the lungs and kidneys were obtained using a Nuclear of Chicago Pho Gamma III camera equipped with a Data-Store/Playback system. Counts of the upper, middle and lower zones of each lung were registered and summated. The relative percent of the total pulmonary arterial blood flow in either lung was

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calculated by the total perfusion of one lung, divided by the sum of both lungs, multiplied by 100 ([right lung/right and left lung] × 100 = percent right lung). Each preoperative lung scan was correlated with the chest roentgenograms, cardiac catheterization data and angiocardiograms. To protect the thyroid, each patient who had not had a recent angiographic study was given Lugol's solution orally (0.3 drops/kg body weight daily, maximal dose 15 drops) for 3 days, commencing at least 1 hour before scanning. No complications resulting from the use of the I^{131}-macroaggregated serum albumin were observed in any patient studied. The results in any given case were essentially reproducible at any given instance when repeated by different technicians.

In this study the pattern of distribution of pulmonary blood flow was considered normal when the distribution to the right lung was 53 ± 2.3 (mean ± standard deviation) of the total concentration of radioactivity and the ratio distribution per unit of lung volume in the upper third was 0.43 ± 0.08.[8] A pattern of pulmonary arterial hypertension was considered present when the upper and lower thirds of the lung showed equal distribution of radioactivity. In 35 infants the changes in the scan patterns before and after surgery were carefully analyzed.

Results

Close correlation was found between the preoperative angiocardiogram and lung scan. The chest roentgenogram showed no such correlation with the angiocardiogram or lung scan. The 53 patients were classified in the following groups: Group I (24 infants with uncomplicated transposition of the great arteries); Group II (18 patients with transposition of the great arteries and ventricular septal defect); and Group III (11 patients with transposition of the great arteries, ventricular septal defect and pulmonary obstruction due either to pulmonary banding [8 patients] or valvular or infundibular stenosis [3 patients]).

Group I: *Preoperatively,* 9 of 17 patients (53 percent) had a normal distribution pattern of pulmonary blood flow. One of these nine patients had a pattern of pulmonary arterial hypertension but normal pulmonary arterial pressure. Among the remaining eight patients, blood flow to the right lung ranged from 56 to 65 percent in one and from 66 to 80 percent in one; two patients manifested preferential blood flow to the left lung of 60 to 80 percent, and in four blood flow distribution could not be calculated because a systemic shunt greater than 70 percent resulted in poor concentration of radioactivity in the lung.

Postoperatively, among the 22 patients studied, the distribution pattern of pulmonary blood flow was normal in 9 patients (41 percent), whereas in 9 blood flow to the right lung ranged from 56 to 65 percent and in 4 (18 percent) from 66 to 80 percent (Table I).

Group II: In 7 (50 percent) of 14 patients preoperative lung scans revealed a normal pattern of distribution of pulmonary blood flow. One of the seven patients had a pattern of pulmonary arterial hypertension, and two with a pulmonary arterial pressure greater than 40 mm Hg had a normal lung distribution pattern. Among the remaining seven patients, blood flow to the right lung ranged from 56 to 65 percent in five patients; three of these had a pattern of pulmonary arterial hypertension but only two of them had a pulmonary arterial pressure greater than 40 mm Hg. In two patients the blood flow distribution could not be evaluated because of a large systemic shunt.

Postoperatively, 5 of 13 patients studied had a normal distribution pattern of pulmonary blood flow. Among the remaining eight patients, in four, including one with a pattern of pulmonary arterial hypertension, blood flow to the right lung ranged from 56 to 65 percent, and in two it ranged from 66 to 80 percent; in two others blood flow to the left lung ranged from 65 to 80 percent (Table I).

Group III: A normal distribution pattern of pulmonary blood flow was found in 5 of 10 patients (50 percent) studied preoperatively. Among the remaining five patients blood flow to the right lung ranged from 56 to 65 percent in one and from 66 to 80 percent in two patients; in two patients the distribution pattern could not be evaluated because of a large systemic shunt and very low level of pulmonary blood flow (Fig. 1A).

Postoperatively, five of eight patients had a normal distribution pattern of pulmonary blood flow (Fig. 1B). Of the remaining three, two had a preferential blood flow to the right lung of 60 percent and one a preferential blood flow to the left lung of 65 percent (Table I). In Group I blood flow distribution to the right lung tended to be slightly greater after operation than before

TABLE I

Pulmonary Blood Flow Distribution in 53 Patients Before and After Mustard Procedure

Percent Blood Flow to Right Lung	Group I*		Group II*		Group III*	
	Preop	Postop	Preop	Postop	Preop	Postop
50–55	9 (53%)	9 (41%)	7 (50%)	5 (38%)	5 (50%)	5 (63%)
55–65	1 (6%)	9 (41%)	5 (36%)	4 (31%)	1 (10%)	2 (25%)
65–80	1 (6%)	4 (18%)	...	2 (15.5%)	2 (20%)	...
20–50	2 (12%)	...	...	2 (15.5%)	...	1 (12%)
Not calculated	4 (23%)	...	2 (14%)	...	2 (20%)	...
Total	17	22	14	13	10	8

*Group I = transposition of the great arteries; Group II = transposition and ventricular septal defect; Group III = transposition, ventricular septal defect and pulmonary obstruction.

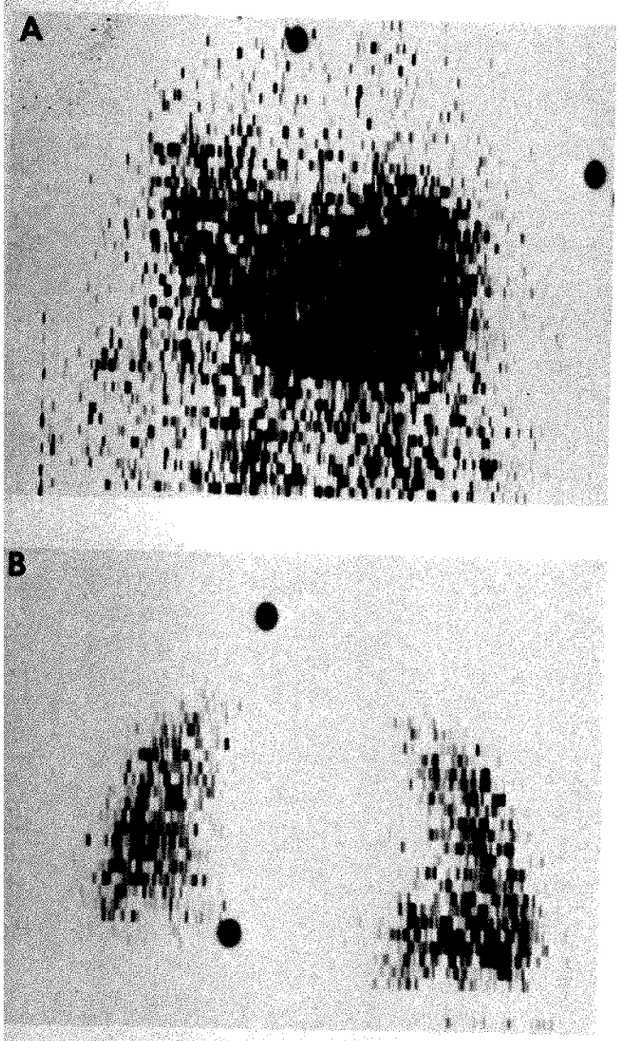
Postop = before operation; preop = after operation.

operation (Fig. 2). In Group II postoperative blood flow distribution to the right lung ranged widely, from 20 to 80 percent (Fig. 3), and in Group III four of five patients had normal values postoperatively (Fig. 4).

Discussion

The rate of accumulation of a substance in any region of the body is directly proportional to the blood flow to the region provided the substance is completely removed from the blood and is not metabolized during the period of observation. To evaluate the pattern of distribution of pulmonary blood flow in patients with transposition of the great arteries before and after complete correction, the distribution of radioactivity in the scintillation lung scan after injection of I^{131}-macroaggregated albumin was utilized. In more than 400 lung scans including the present series with I^{131}-macroaggregated albumin no complications have been found in our patients with either a right to left or left to right shunt. A good correlation between pulmonary arterial blood flow determined by the perfusion lung scan and cardiac catheterization and angiocardiographic findings was found by others[5,8,12–14] and by us in this series. A normal distribution of pulmonary blood flow was found preoperatively in 21 of our patients with transposition of the great arteries whereas 10 had preferential flow to the right lung and 2 had preferential flow to the left lung. Postoperatively, 19 patients had a normal flow pattern, whereas 21 had preferential flow to the right lung and 3 had preferential flow to the left lung. When this group of patients was separated into patients with uncomplicated transposition (Group I), transposition with ventricular septal defect (Group II) and transposition with ventricular septal defect and pulmonary arterial obstruction either by pulmonary arterial banding or subpulmonary stenosis (Group III), no significant difference was found among groups in the proportion of different patterns of pulmonary blood flow distribution.

In nine patients the preoperative pulmonary blood flow pattern could not be evaluated because of a large systemic shunt leading to a low level of pulmonary blood flow and consequently a very low level of lung radioactivity. No patient had postoperative evidence of a systemic shunt. Pulmonary arterial hypertension may result in an abnormal distribution of radioactivity in the lung field.[5] However, we found no close correlation between the classic pattern of pulmonary arterial hypertension and pulmonary arterial pressure. Pulmonary



GURE 1. Lung scans in a patient with transposition of the great arries, ventricular septal defect and pulmonary stenosis (Group III). **A**, eoperative, showing a high level of radioactivity in the heart and alost no radioactivity in the lung field. **B**, postoperative, showing a rmal lung scan.

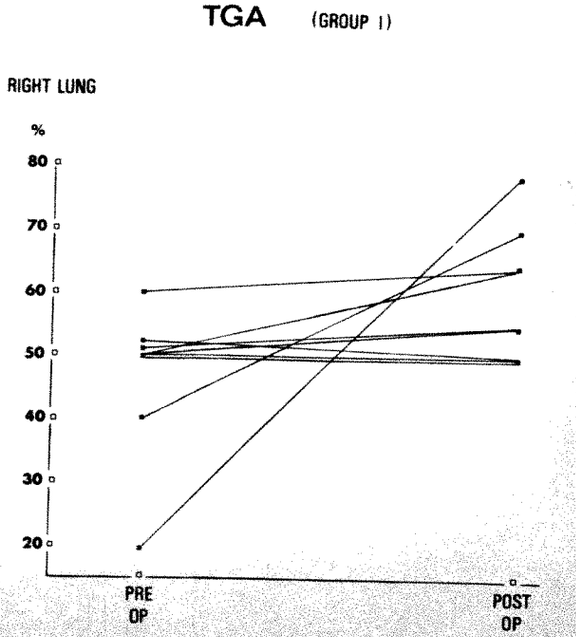


FIGURE 2. Group I. Pre- and postoperative pulmonary blood flow distribution in nine patients with transposition of the great arteries who underwent Mustard's procedure for correction.

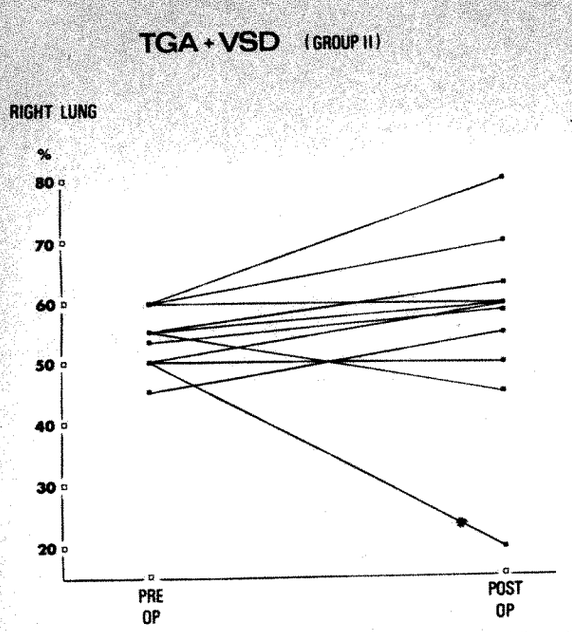


FIGURE 3. Group II. Pre- and postoperative pulmonary blood flow distribution in 11 patients with transposition of the great arteries and ventricular septal defect who underwent Mustard's procedure for complete correction.

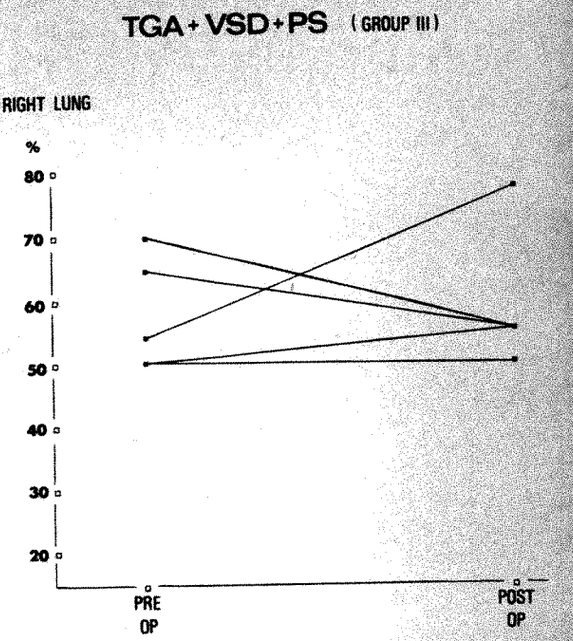


FIGURE 4. Group III. Pre- and postoperative pulmonary blood flow distribution in five patients with transposition of the great arteries and ventricular septal defect and pulmonary obstruction who underwent Mustard's procedure for complete correction.

venous hypertension, on the other hand, causes a characteristic redistribution of pulmonary blood flow and abnormal perfusion scans.[5] Therefore, the postoperative lung scans in the diagnosis of venous obstruction after Mustard's procedure should be useful. No patient in our series had signs of pulmonary venous obstruction in the postoperative lung scan.

Correlation of chest roentgenogram, lung scan and angiocardiogram: Muster et al.[14] reported correlation of the chest roentgenogram, lung scan and angiocardiogram in five infants with diminished left pulmonary flow in transposition of the great arteries not suspected from the chest roentgenogram before angiography. Lung scans in these five patients corroborated the angiographic finding, showing a mean uptake for the group of 22 percent in the left and 78 percent in the right lung. Muster et al.[14] considered two mechanisms for this unequal distribution of pulmonary blood flow: (1) The existence in transposition of an unusual angulation of the right and left pulmonary arteries at their junction with the main pulmonary artery may result in preferential flow to the right pulmonary artery and (2) a Coanda effect generated in transposition by accelerated blood flow across the left ventricular outflow tract may favor bloodstreaming along the right wall of the pulmonary artery. In our series, we also found no correlation between the chest roentgenogram and either the lung scan or angiocardiogram, but a close correlation between the lung scan and angiocardiogram. The inability of the chest roentgenogram to show the unequal distribution of pulmonary blood flow could be explained by the large shunt and low pulmonary flow level present in our patients. Nevertheless, as a screening procedure and for a serial study of the effects of surgical intervention, the lung scans provide physiologic and anatomic information.

Clinical applications: The atraumatic and noninvasive nature of this examination deserves special emphasis in the pediatric age group. This procedure can easily be performed on an outpatient basis and therefore removes from the patient, parents and physicians, psychologic burdens associated with hospitalization for collection of follow-up data on a child who is otherwise doing well.

We have found this procedure to be helpful in follow-up studies to rule out (1) recurrence of a systemic shunt of transposition after correction or (2) possible development of pulmonary venous hypertension. This method is technically simple, without risk, easily applicable to large numbers of patients and provides important postoperative follow-up information. All patients in our institution with cyanotic congenital heart disease are now studied preoperatively by scintillation lung scan.

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Echocardiographic Localization of Interatrial Baffle After Mustard Operation for Dextrotransposition of the Great Arteries

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The position of the interatrial baffle was determined by echocardiography in 11 patients with complete transposition of the great arteries who had undergone the Mustard operation. The location of the interatrial baffle and the newly created systemic venous atrium and the pulmonary venous atrium behind the pulmonary arterial root was established by echocardiographic contrast studies during cardiac catheterization. Angiographic analysis indicated that the segments of the systemic and pulmonary venous atria seen behind the pulmonary arterial root in the echocardiogram were, respectively, the superior limb of the systemic venous atrium and the posterior segment of the pulmonary venous atrium. The area of mitral-pulmonary valve continuity in the echocardiogram was used as a reference point for dimensional measurements of the systemic and pulmonary venous atria. It is suggested that longitudinal measurements of these structures by echocardiogram may help evaluate their growth in size. Fine to coarse fibrillatory movements of the atrioventricular valves and, more frequently, of the mitral valve were seen in the majority of patients.

The echocardiogram has been reported to have diagnostic value in transposition of the great arteries.[1] The left ventricle and pulmonary arterial root can be studied by echocardiography with reproducible accuracy. Surgical correction of transposition of the great arteries with the Mustard technique involves placement of an interatrial baffle that directs superior and inferior vena caval blood flow to the left ventricle and pulmonary venous blood flow to the right ventricle.[2] Follow-up studies of the size of the systemic venous atrial chamber created by the interatrial baffle are important in a growing child to determine whether the atrium is continuing to grow and provide an adequate chamber for increasing venous return.

The purpose of this study was to determine whether the echocardiogram could be used to identify and localize the position of the interatrial baffle and the newly created systemic and pulmonary venous atrial chambers and to assess their dimensions noninvasively. The effect of the Mustard operation on atrioventricular (A-V) valve motion was also examined.

Material and Methods

Eleven patients with dextrotransposition of the great arteries were studied by echocardiography after they had undergone the Mustard operation and correction of any associated lesions. Of the six patients with associated lesions, three had a ventricular septal defect, two a ventricular septal defect with left ventricular outflow tract stenosis and one an intact ventricular septum with left ventricular outflow tract stenosis. Pericardial tissue was used to construct the interatrial baffle in all 11 patients. Echocardiograms were recorded using commercially available Ekoline (Smith-Kline) or Rohe ultrasonic units. A 2.25 me-

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gahertz transducer was positioned in the third or fourth intercostal space and its angulation and distance from the sternum varied. In nine children, the echocardiograms were obtained during or immediately after cardiac catheterization studies undertaken to assess the adequacy of the Mustard operation (Table I).

The location of the baffle and a segment of the systemic venous atrial chamber was determined with echocardiographic contrast studies during cardiac catheterization. The systemic venous atrium was delineated by the appearance of clouds of echoes after the rapid injection of 5 to 10 ml of saline solution through the catheter placed in that chamber.

A relatively reproducible echocardiographic dimension of these structures was obtained by identifying the point of mitral-pulmonary valve continuity, a point of reference. The diameter of the pulmonary arterial root was measured at end-systole just distal to this reference point. The echoes of the superior limb of the systemic venous atrium and the posterior segment of the pulmonary venous atrium were also well established just proximal to the point of mitral-pulmonary valve continuity, and their dimensions were measured at end-systole (Fig. 1). These measurements represent a relatively anteroposterior dimension of these structures. In seven of the nine patients who underwent cardiac catheterization studies, the echocardiographic measurements of the systemic venous atrium were correlated with the angiographic anteroposterior dimensions of the superior limb of this chamber at a level immediately posterior to the pulmonary arterial root (Fig. 2). In the remaining two patients (Cases 3 and 7) angiograms satisfactory for analysis were not available. Angiographic magnifications were corrected using the image size of the catheter in the systemic venous atrium.

TABLE I

Echocardiographic Data in 11 Patients After Mustard Operation for Transposition of the Great Arteries

Case no.	Age (mo)		BSA at Echo Study (m^2)	Atrial Chamber Dimension (cm)		Pulmonary Arterial Root Diameter (cm)	Pressure Gradient* (mm Hg)
	At Operation	At Echo Study		Systemic Venous	Pulmonary Venous		
1	68	68	0.58	0.60	0.9	1.4	. . .
2	108	108	1.00	0.90	2.0	3.0	. . .
3	19	98	0.93	0.80	1.4	2.5	14†
4	29	59	0.71	0.80	1.0	1.6	16
5	19	48	0.60	0.85	1.0	1.3	8
6	30	80	0.90	0.80	1.0	2.0	22
7	32	74	0.80	0.80	1.5	2.8	24†
8	23	50	0.71	0.60	1.0	1.8	36
9	36	96	0.72	1.20	1.4	1.8	4†
10	81	126	1.10	1.20	1.3	2.4	20
11	18	54	0.68	0.60	0.8	2.0	10
Range	18–108	48–126	0.58–1.10	0.6–1.2	0.8–2.0	1.3–3.0	

*Peak systolic pressure gradient across left ventricular outflow tract.
†Patients with systolic anterior motion of mitral valve.

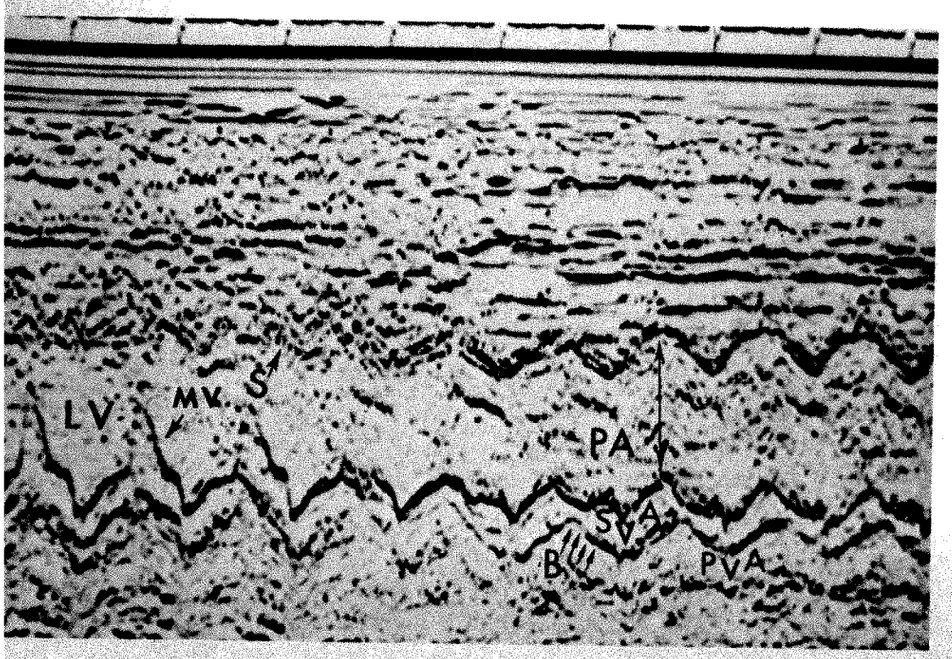

FIGURE 1. Case 11. Echocardiogram obtained by scanning from the pulmonary arterial root (PA) toward the left ventricle (LV). Note the continuity of the posterior pulmonary arterial wall with the anterior leaflet of the mitral valve (MV). Echoes of the interatrial baffle (B) are located behind the posterior wall of the pulmonary arterial root and establish dimensions of the systemic venous atrial chamber (SVA). Echoes of the posterior wall of the pulmonary venous atrial chamber (PVA) are posterior to the baffle echoes. Both echoes end near the mitral valve anulus. Arrows indicate position of various structures. S = interventricular septum.

Results

Echocardiographic localization of systemic venous atrium: The pericardial interatrial baffle forming the systemic venous atrium was recognized as an abnormal linear echo behind the pulmonary arterial root, located approximately halfway between the posterior wall of the pulmonary artery and the posterior wall of the pulmonary venous atrium; this observation confirms recent findings.[3] Scanning from the pulmonary artery to the left ventricle demonstrated continuity of the posterior pulmonary arterial wall with the mitral valve, whereas the interatrial baffle echo ended near the mitral valve anulus (Fig. 1). Ultrasonic contrast studies during cardiac catheterization confirmed that the area between the posterior pulmonary arterial wall and the interatrial baffle was indeed the systemic venous atrium. The location of this atrium was further verified by the rapid sequential appearance of the echoes in the pulmonary artery (Fig. 3). We have now been able to locate these structures consistently in patients with transposition who have had the Mustard operation.

Cardiac catheterization findings: Nine of the 11 patients were restudied with cardiac catheterization after the Mustard operation, and all were considered to have satisfactory repair (Table I). In two children (Cases 3 and 7), mild pulmonary venous obstruction was demonstrated by the presence of a mean pressure gradient of 8 and 10 mm Hg, respectively, between the pulmonary arterial wedge pressure and mean pressure in the pulmonary venous atrium. Pulmonary arterial pressures in both patients were normal. A mild peak systolic pressure gradient (10 to 24 mm Hg) was noted across the left ventricular outflow tract in seven of the nine patients studied. One patient (Case 8) had a moderate pressure gradient (36 mm Hg) from the left ventricle to the pulmonary artery and one (Case 9) had no significant gradient. Significant superior or inferior vena caval obstruction was not noted in any of these patients, and the maximal mean pressure gradient between the inflow caval vessels and the systemic venous atrium was 4 mm Hg, noted in two patients (Cases 4 and 9).

Echocardiographic dimensions (Table I): The mean interval between Mustard repair and echocardiographic study was 36.2 months (range 27 to 79). The mean echocardiographic dimension of the systemic venous atrium as measured behind the pulmonary arterial root echo was 0.83 cm (range 0.58 to 1.10). In seven patients, a reasonable agreement was noted between echocardiographic and angiographic dimensions of the systemic venous atrium when this chamber was measured behind the pulmonary arterial root (Fig. 4). The mean amplitude of the baffle movement was 5.3 mm (range 3 to 8). Baffle movements were primarily anterior during systole although both anterior and posterior movements occurred during some systolic and diastolic phases of the cardiac cycle.

The pulmonary arterial root dimensions demonstrated relatively linear correlation with body surface area, but neither the systemic venous atrial dimension

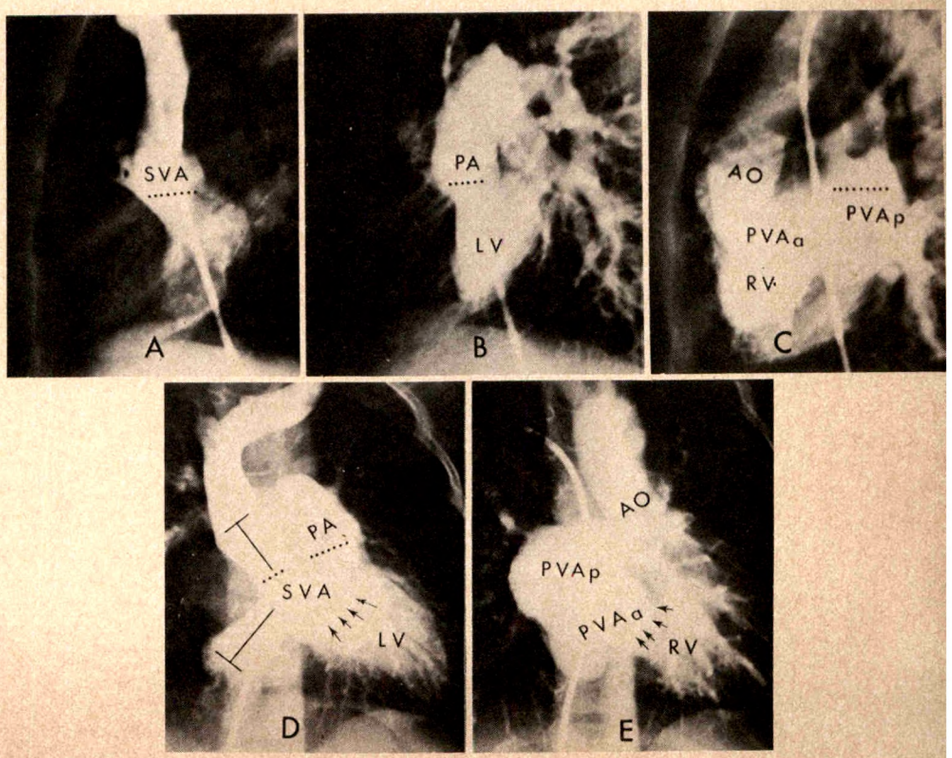

FIGURE 2. Case 11. Lateral views of superior vena caval angiograms. **Panels A** to **C** show sequential opacification of the systemic venous atrium (SVA), left ventricle (LV) and pulmonary artery (PA). Levophase film **(panel C)** shows opacification of the posterior segment of the pulmonary venous atrium (PVAp) and its anterior segment (PVAa). Finally, the right ventricle (RV) and aorta (AO) are opacified. Anteroposterior views **(panels D** and **E)** further elucidate the anatomic configuration of the systemic **(panel D)** and the pulmonary **(panel E)** venous atria. T bars **(panel D)** indicate the superior and inferior limbs of the systemic venous atrium. **Multiple arrows** indicate the position of the mitral **(panel D)** and tricuspid **(panel E)** valves. The **dotted lines** in both views indicate the areas presumed to be traversed by the echocardiographic beam.

nor the posterior segment dimension of the pulmonary venous atrium showed such correlation in this small population sample (Fig. 5).

Atrioventricular valve movements: Atrioventricular (A-V) valve movements were abnormal in most of the 11 patients. The mitral valve in 8 patients showed fine to coarse fibrillatory movements of both the anterior and posterior leaflets during diastole (Fig. 6). In some strip chart recordings, this abnormality appeared to be intermittent or cyclic in the continuous record. Similar coarse fibrillatory movements of the tricuspid valve were noted less frequently (4 patients). The mean amplitude of mitral valve movement was 1.8 cm (range 1.2 to 2.5). In three patients, systolic anterior motion of the mitral valve was present in various degrees; two of these patients (Cases 3 and 7) had a mild left ventricular outflow tract pressure gradient of 14 and 24 mm Hg, respectively.

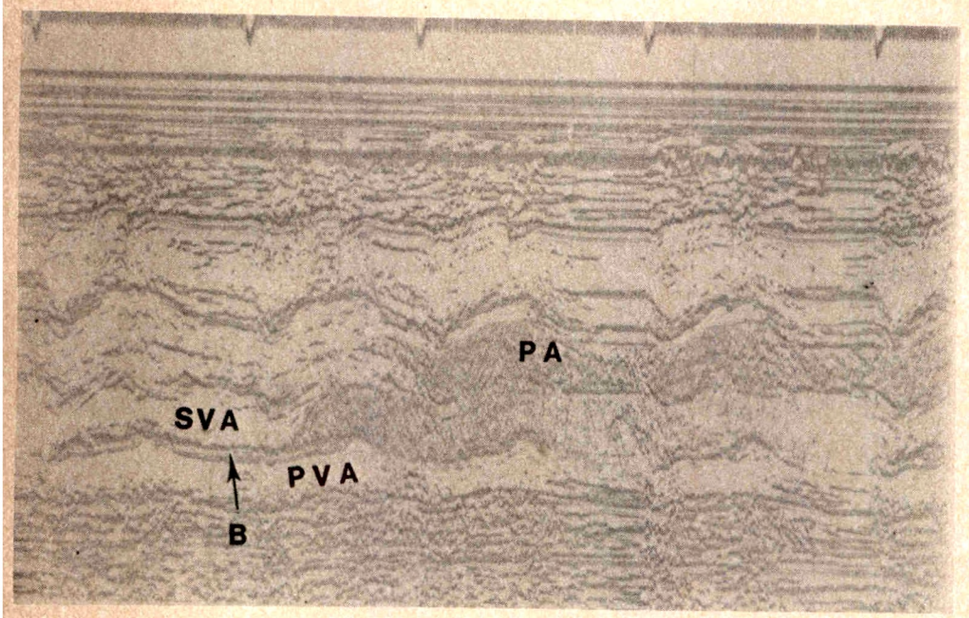

FIGURE 3. Case 4. Echocardiogram showing the systemic venous atrial chamber (SVA) behind the posterior wall of the main pulmonary artery (PA). Injection of saline solution into the inferior vena cava results in clouds of echoes appearing first in the systemic venous atrial chamber and thereafter in the pulmonary artery. The pulmonary venous atrium (PVA) is posterior to the systemic venous atrium. B = atrial baffle.

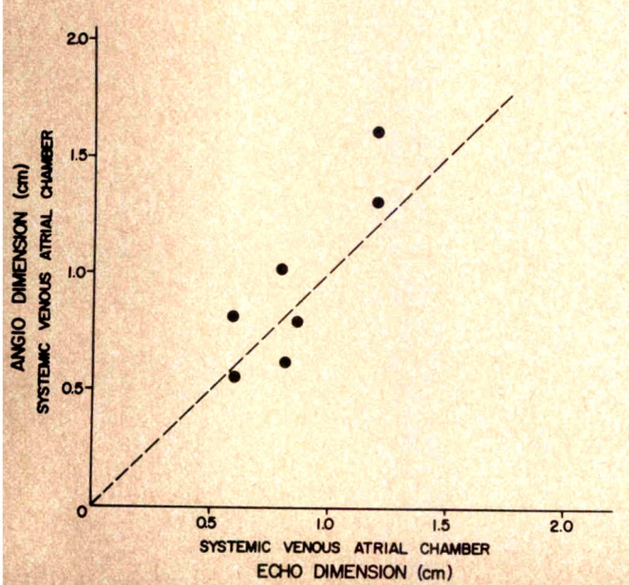

FIGURE 4. Anteroposterior dimensions of the superior limb of the systemic venous atrial chamber by echocardiographic (ECHO) and angiographic (ANGIO) methods in seven of nine patients studied with cardiac catheterization studies.

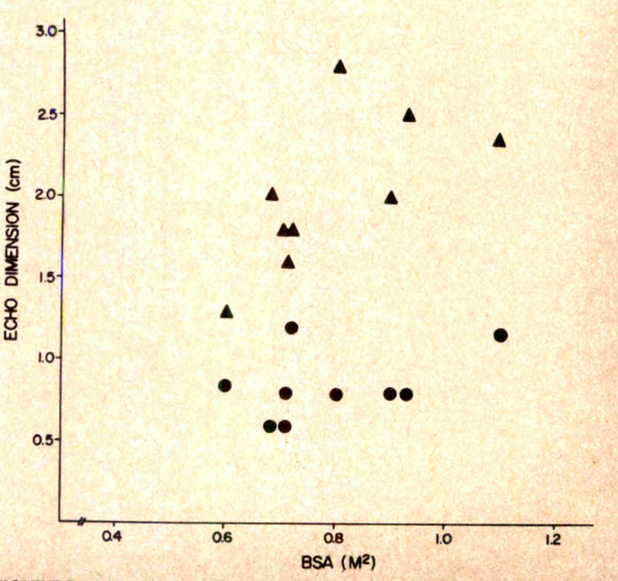

FIGURE 5. The anteroposterior dimension of the pulmonary arterial root **(triangles)** bears a statistically significant relation to body surfact area ($r = 0.68$) in nine patients studied with cardiac catheterization. This relation is not present for the newly created systemic venous atrial chamber **(circles)** in these patients.

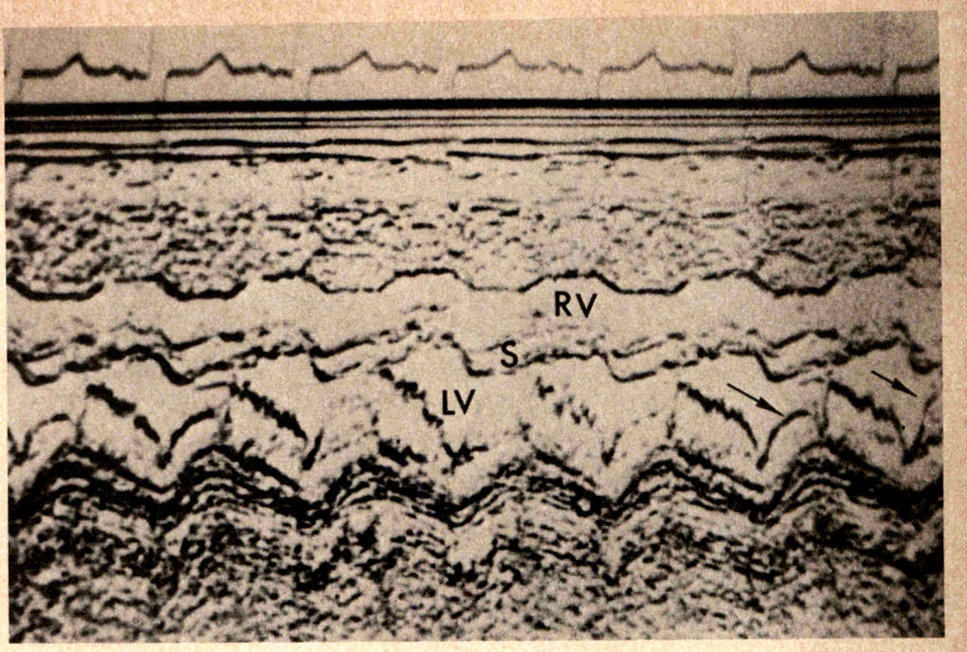

FIGURE 6. Case 9. Echocardiogram demonstrating fine and coarse fibrillating movements of the mitral valve leaflets after the Mustard operation for transposition of the great arteries. Varying degrees of systolic anterior movement of the mitral valve are also evident **(arrows).** LV = left ventricle; RV = right ventricle; S = interventricular septum.

Discussion

Echocardiographic and angiographic correlations: Our data indicate that the interatrial baffle can be consistently located behind the pulmonary arterial root with ultrasound and, furthermore, that a dimension of the new systemic venous atrium and the posterior segment of the pulmonary venous atrium can be measured with reliable accuracy using mitral-pulmonary valve continuity as a reference point. In one recent study,[3] although the baffle could be seen behind the tricuspid valve and aortic root in the echocardiogram of some patients, it was most consistently recorded behind the pulmonary arterial root. The systemic venous atrial echocardiographic dimension, as measured behind the pulmonary arterial root, probably represents a measurement of the superior limb of the newly fashioned systemic venous atrial chamber (Fig. 2). We found an apparent correlation between the echocardiographic and angiographic dimensions of these structures; however, the angiographic dimensions of the systemic venous atrium were greater than the echocardiographic dimension in most patients. Since the two measurements undoubtedly represent somewhat different beam projections, and hence dimensions, it is not surprising that some differences are present.

It is not likely that these dimensions adequately reflect the full size of the new systemic and pulmonary chambers, but they do appear to be reproducible and have appropriate identifying landmarks in the echocardiogram. The created systemic venous atrium does not have a simple geometric shape but is a complex two-limbed expanding structure coursing leftward and posteriorly toward the mitral valve. From angiographic comparisons, it appears that the echocardiographic dimensions of the systemic venous atrium represent a measurement of the lower portion of the superior limb of that chamber. The dimensions of this portion appeared to be smaller than those of the rest of this chamber (Fig. 2), particularly near the mitral valve, as demonstrated with angiography. Similarly, the echocardiographic dimensions obtained from the posterior segment of the pulmonary venous atrium do not represent the maximal diameter of this chamber but rather a minor axis of what appears to be a relatively oval structure (Fig. 2). It is likely that other echocardiographic views and dimensions of these structures can be obtained with other probe positions.

Our limited initial echocardiographic observations indicate that the pulmonary arterial root grows in proportion to body surface area; however, the systemic venous atrial dimension shows no such correlation, suggesting that this chamber may not grow in proportion to body size. Repeated longitudinal measurements of these dimensions obtained from the pulmonary arterial root, the systemic venous atrium and posterior pulmonary venous atrium may permit noninvasive observation of the growth patterns of these structures.

Significance of abnormal A-V valve movements: The fine to coarse diastolic fibrillatory movements of the A-V valves were not clearly related to any observed hemodynamic factors; their presence confirms recent reports[3,4] of abnormal A-V valve movement after the Mustard operation. These coarse movements may result indirectly from the relatively low level of compliance of the systemic venous atrium and the decreased size of the pulmonary venous atrium. The systemic venous return from the superior and inferior venae cavae normally drains into a large compliant right atrium. However, the systemic venous atrium created by the Mustard operation is smaller and less compliant, as suggested by the limited systolic and diastolic baffle movements ob-

served. As a consequence of this limited compliance and smaller volume, systemic venous blood flow velocity at the mitral valve orifice would be increased, resulting in greater turbulence and, hence, vibrations and irregular fibrillatory movements. The cyclic or intermittent nature of these movements noted in some of our tracings might well be related to the inspiratory increase in systemic venous return, which produces greater velocity of blood flow at the mitral valve site.

Systolic anterior motion of the mitral valve has been reported both before and after the Mustard operation in patients with transposition of the great arteries and has been correlated with left ventricular outflow tract stenosis.[5] However, although most of our patients had mild left ventricular stenosis, only a few manifested systolic anterior motion of the mitral valve. Moreover, this motion was observed even in patients with no significant left ventricular outflow tract stenosis.

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Echocardiographic Detection of Large Left to Right Shunts and Cardiomyopathies in Infants and Children

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Diagnostic separation of infants with signs of cardiac failure (hypoglycemia, sepsis, myocarditis, hypoxemia) but no congenital cardiocirculatory malformation from those with a large left to right shunt is crucial in newborn management. Echocardiographic studies of 218 infants and children allowed group separation and distinction from normal by the assessment of mean velocity of circumferential fiber shortening (Vcf) and the ratio of left atrial to aortic root diameter at end-systole (LA/Ao). In normal premature and full-term infants, Vcf (1.51 ± 0.04 [mean ± standard error]) was significantly lower than in infants with a large shunt (2.12 ± 0.08, $P < 0.01$) and higher than in infants with nonstructural heart disease (1.18 ± 0.06, $P < 0.001$). LA/Ao ratios were comparable in the groups with a large shunt and nonstructural heart disease (1.14 ± 0.1 and 1.26 ± 0.2, respectively) and were significantly higher in both groups than in normal subjects (0.77 ± 0.01, $P < 0.001$). Similar echocardiographic distinctions could be made when 10 older children (aged 2 to 10 years) with cardiomyopathy were compared with 45 normal older children. Serial determination of these variables was of major assistance in patient management.

Since the development of high frequency ultrasonic transducers and continuous recording techniques, echocardiography has achieved increasing prominence as an aid in the evaluation and management of infants and children with heart disease. In the pediatric age group, ultrasonic techniques have been applied most frequently to detect structural cardiac malformations.[1–3] In contrast, there is little information concerning the noninvasive evaluation of cardiocirculatory function in normal infants and children or those with disease affecting cardiac function in spite of normal cardiac anatomy. Previous studies from our laboratory have provided a range of normal values for cardiac and great vessel dimensions and mean rate of left ventricular circumferential fiber shortening in infants.[4,5] This investigation extends the range of normal values to include older children for whom no previous data exist. In addition, this study evaluates the usefulness in differential diagnosis and patient management of the echocardiographically derived mean value for left ventricular circumferential fiber shortening and the ratio of left atrial to aortic root diameter. The study groups include normal infants and children, those with a large or small left to right shunt, and those with nonstructural heart disease.

Methods

Echocardiographic studies were performed in 218 infants and children using commercially available ultrasonoscopes, Picker 103 or a Smith-Kline Ekoline-20A, interfaced with a Honeywell 1856 fiberoptic stripchart recorder. A 5 megahertz, 0.25 inch (0.64 cm) nonfocused transducer was employed. The site of maximal mitral valve excursion was identified by sweeping the transducer beam within the left ventricle from its body to the outflow tract (Fig. 1). When a suitable study of left ventricular and left ventricular outflow tract anatomy was obtained, the following variables were measured:

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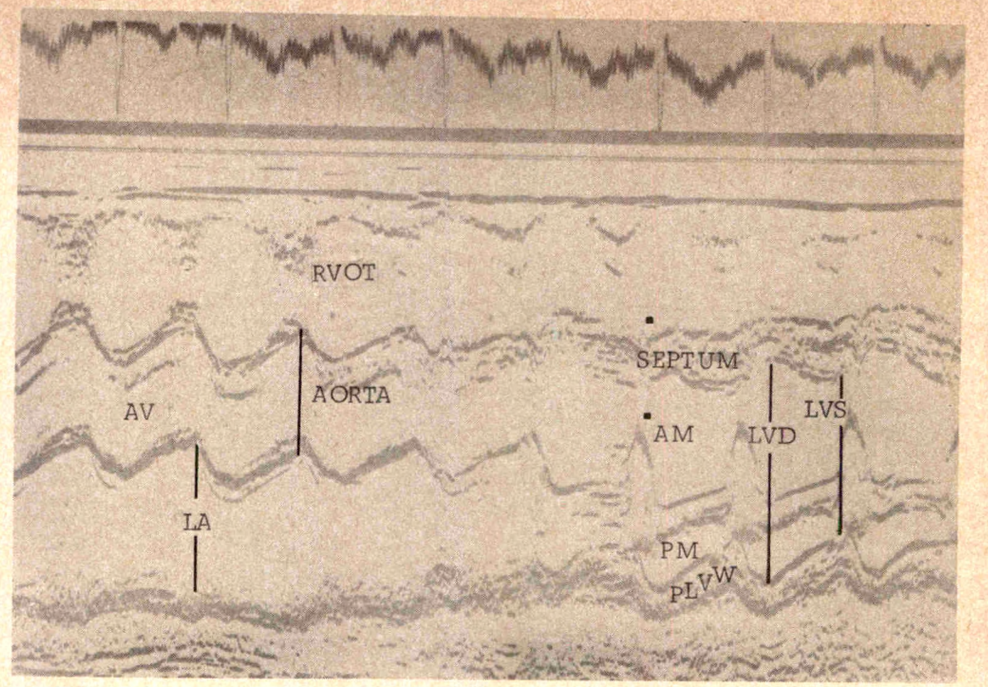

FIGURE 1. An M-mode scan of the left ventricle from the body to the outflow tract and the aortic root in a patient with a ventricular septal defect. The left atrial (LA) dimension is slightly enlarged. The left ventricular diastolic (LVD) and left ventricular systolic (LVS) dimensions are shown **(vertical lines)** as well as the measurement of the aortic root. The electrocardiogram is at the top of the tracing. AM = anterior mitral valve leaflet; AV = aortic valve; PLVW = posterior left ventricular wall; PM = posterior mitral valve leaflet; RVOT = right ventricular outflow tract.

1. Left atrial dimension was determined at end-systole as the distance between the outer edge of the posterior aortic root echo and the left atrial wall endocardial echo. This dimension was measured behind an area of the aortic root in which cusp tissue was imaged and in an area where the left atrial endocardial echo was single and discrete.

2. Aortic root dimension was measured as the distance between the outer walls of the aortic root at end-systole. This measurement was obtained during the same or adjacent cardiac cycle as that in which left atrial dimension was calculated.

Because a wide range existed in absolute left atrial and aortic root diameters in infants of similar size,[4] these dimensions are expressed in this report as the ratio between the left atrial and aortic dimension (LA/Ao). Errors introduced by small differences in measurement of the absolute dimensions of the left atrium or aortic root may be minimized when the data are expressed as a left atrial/aortic ratio since changes caused by obliquity of the ultrasonic beam yield proportionate enlargement of both structures.

*3. Mean Vcf** was determined, as previously described,[5] from end-diastolic and end-systolic left ventricular diameters using mitral valve motion for timing purposes. The paper speed in all these examinations was either 50 or 100 mm/sec, and ejection time was measured from the mitral valve complex to the nearest 10 msec. The validity of this technique is reviewed in detail in the Discussion section.

The following groups of infants and children were studied:

Infants

1. Seventy normal full-term infants (average weight 2,850 g) and 25 healthy premature infants aged 24 to 96 hours (average weight 1,740 ± 82 [standard error] g). Data from full-term infants and healthy premature infants were combined since no statistically significant differences existed between them.

2. Fifteen premature infants (aged 72 to 150 hours, average weight 1,464 ± 84 g) who had a moderate to severe respiratory distress syndrome[6] and no physical signs of a patent ductus arteriosus. Although we appreciate that left to right ductal flow may occur without an audible murmur in these premature infants, precordial activity and peripheral pulses were normal. All of these infants had endotracheal intubation and positive pressure ventilation and had maintained an arterial oxygen tension in excess of 45 mm Hg for at least 12 hours before echocardiographic study.

3. Twenty premature infants (aged 2 days to 3 weeks, average weight 1,416 ± 88 g) with a systolic heart murmur and clinical evidence of a large patent ductus arteriosus. Each infant in this group was fully digitalized and was receiving maintenance doses of digoxin (average 15 μg/kg daily). Thirteen infants underwent operative ligation and eight had postoperative echocardiographic investigations while still receiving digitalis. None underwent hemodynamic study. At operation each had a ductus arteriosus with an external diameter approximately equal to that of the descending aorta.

4. Eight infants (aged 2 to 6 months, weight 2.5 to 6.5 kg) who had a ventricular septal defect and a large left to right shunt (Qp/Qs > 2:1) demonstrated at cardiac catheterization. All of these infants were receiving maintenance doses of digoxin (15 μg/kg daily).

5. Seven infants (aged 4 days to 6 months, weight 1,460 to 4,810 g) judged clinically to have either a hemodynamically insignificant patent ductus arteriosus or a small ventricular septal defect. Each of these patients was in a clinically stable condition and had received no cardiac medications.

6. Ten infants (aged 4 hours to 3 weeks, average weight 2,320 g) who had acute viral myocarditis (no. = 4), severe hypoglycemia (blood glucose less than 25 mg/100 ml) (no. = 5) or sepsis (no. = 1) with cardiomegaly and clinical signs of cardiac decompensation that prompted the administration of digoxin.

$$^{*}\text{Vcf} = \frac{\text{left ventricular end-diastolic dimension (mm)} - \text{end-systolic dimension (mm)}}{\text{end-diastolic dimension (mm)} \times \text{ejection time (sec)}}$$

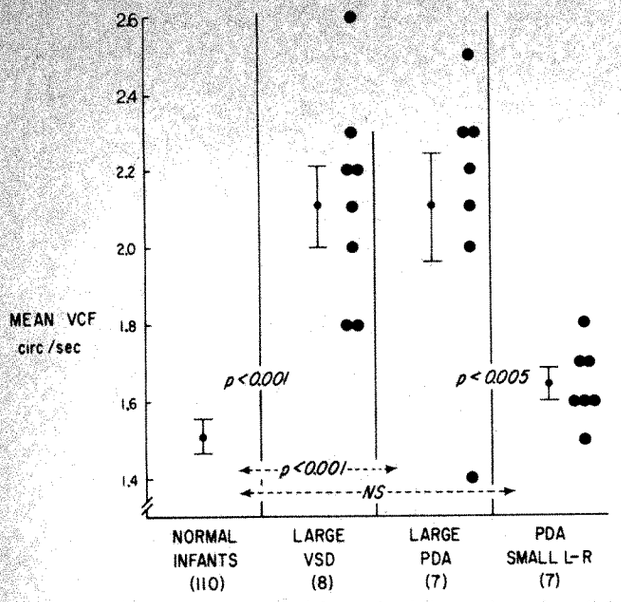

FIGURE 2. Echocardiographically determined mean circumferential fiber shortening rate (VCF) for normal infants (combining data for normal full-term infants, healthy premature infants and premature infants with respiratory distress) and for infants with small and large left to right (L–R) shunts. The **points** and **vertical bars** at the left of each column represent the mean ± standard error. The numbers in parentheses indicate the number of infants in each group. Individual patient values **(closed circles)** are shown for the abnormal infants at the right of each column. The highest and lowest mean Vcf values encountered in the normal infant group were 2.0 and 1.3 circumferences/sec, respectively. PDA = patent ductus arteriosus, unoperated on; VSD = ventricular septal defect.

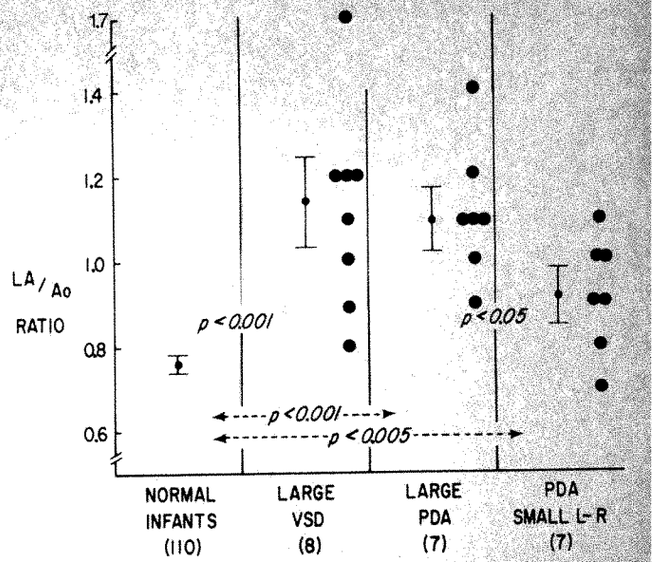

FIGURE 3. Echocardiographically determined left atrial/aortic root dimension ratios (LA/Ao) for the normal infants and infants with a left to right (L–R) shunt. The highest and lowest LA/Ao ratios encountered in the normal infants were 1.1 and 0.5, respectively, each in one infant. Symbols and abbreviations as in Figure 2.

Children

1. Forty-five normal children (aged 3.6 ± 0.4 years, range 2 to 10).

2. Seven children (aged 4.2 ± 0.6 years, range 2 to 10) with a clinical diagnosis of idiopathic cardiomyopathy of the dilated type (no. = 5) or enteroviral myocarditis (no. = 2). The five children with idiopathic cardiomyopathy had electrocardiographic and radiologic evidence of cardiomegaly or cardiomyopathy, and two had decreased left ventricular contractility demonstrated during hemodynamic study in the absence of structural heart disease. No patient in this group was treated with digitalis at the time of the initial echocardiographic study.

Digitalis Group

3. Eleven infants and children with diverse diagnoses (see Fig. 7: ventricular septal defect, large left to right shunt [no. = 4]; small ventricular septal defect [no. = 3]; cardiomyopathy [no. = 4]) studied before and after oral or intravenous administration of digitalis (total dose 35 to 45 μg/kg over 24 hours) to determine the magnitude of change in Vcf produced by this intervention.

Student's *t* test was employed to assess statistical significance.

Results

Infants

No significant differences existed in mean values for velocity of circumferential fiber shortening (Vcf) or ratio of left atrial to aortic root diameter (LA/Ao) among the normal full-term infants (mean Vcf = 1.5 ± 0.04, LA/Ao = 0.78 ± 0.01), 25 healthy premature infants (mean Vcf = 1.62 ± 0.11, LA/Ao = 0.73 ± 0.03) and the 15 infants with respiratory distress syndrome (mean Vcf = 1.44 ± 0.14, LA/Ao = 0.76 ± 0.04). Thus, combining all of these data yielded an average value of mean Vcf of 1.51 ± 0.04 and LA/Ao ratio of 0.77 ± 0.01 (Fig. 2 and 3). Heart rate in the normal premature and full-term infants averaged 120 ± 18 beats/min that in the infants with the respiratory distress syndrome was 140 ± 14 beats/min.

Left to right shunts: In infants with a large left to right shunt through a ventricular septal defect or patent ductus arteriosus, mean Vcf was significantly greater than normal (2.12 ± 0.08, and 2.10 ± 0.14, respectively, $P < 0.001$) (Fig. 2). The average heart rate in these infants was 141 ± 15 beats/min. In this group both an increase in end-diastolic dimension and an augmented extent of left ventricular circumferential shortening are of major importance in producing the elevated values of mean Vcf. Since average heart rates were the same for the group with a left to right shunt and the normal group, it is unlikely that differences in heart rate could account for the differences in Vcf. Nevertheless, a shortened ejection time may be of some importance. Unfortunately, reliable weight-related data for absolute left ventricular end-diastolic dimension in small premature infants are unavailable for comparison with this study group. The mean Vcf in the infants with a small left to right shunt (1.63 ± 0.04) was similar to the normal value and significantly lower than that of the group of infants with a large shunt ($P < 0.005$). LA/Ao ratio data are illustrated in Figure 3. This ratio was significantly elevated ($P < 0.001$) in infants with a large ventricular septal defect or a large patent ductus arteriosus (1.14 ± 0.11 and 1.09 ± 0.06, respectively). In infants with a

small left to right shunt, the LA/Ao ratio (0.92 ± 0.06) was intermediate between that of the normal group and the group with a large shunt and was statistically different from the latter only ($P < 0.05$).

Surgical ligation of a patent ductus arteriosus was performed in 13 infants. In 8 of the 13, serial pre- and postoperative echocardiograms were available (Fig. 4). This group of surgically treated patients consists of a separate later group of infants from both the University of California and the University of Arizona, and they have a higher preoperative LA/Ao ratio than that of the California infants with patent ductus arteriosus whose data are shown in Figure 3. This contrast is the result of differences between the two centers in clinical protocols of patient management. The surgically treated infants were studied within 12 hours of operation while receiving digoxin. A dramatic reduction in the preoperative LA/Ao ratio (1.7 ± 0.15) was noted postoperatively (LA/Ao ratio = 0.96 ± 0.05, $P < 0.001$). An insignificant mean decline was observed in mean Vcf (from 2.11 ± 0.16 before to 1.6 ± 0.2 within 2 to 12 hours after operation, P = not significant).

Nonstructural heart disease: Data from infants with normal cardiac anatomy but with problems capable of altering cardiocirculatory function (sepsis, myocarditis, hypoglycemia) are shown in Figure 5. All of these infants were receiving maintenance doses of digitalis at the time of echocardiographic study. When compared with values in normal infants, mean Vcf (1.18 ± 0.06) was significantly reduced; although there was

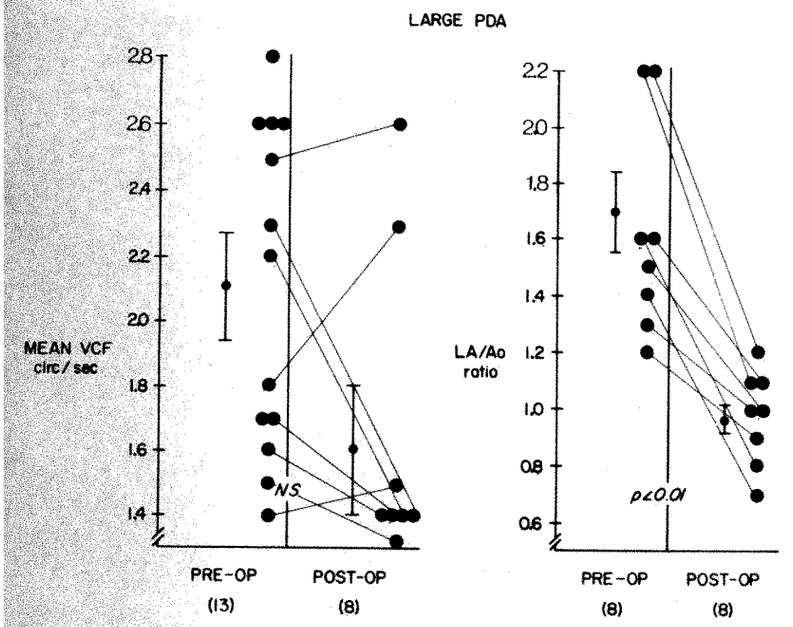

FIGURE 4. Serial mean circumferential fiber shortening rate (VCF) and left atrial/aortic root (LA/Ao) dimension data from infants before (PRE-OP) and within 12 hours after (POST-OP) ligation of a patent ductus arteriosus (PDA). Individual patient values **(closed circles)** are shown on the right of each column. Pre- and postoperative measurements are connected by a line for the infants studied serially. The number of patients in each group is shown in parentheses. Each **point** and the **vertical bars** represent the mean ± standard error.

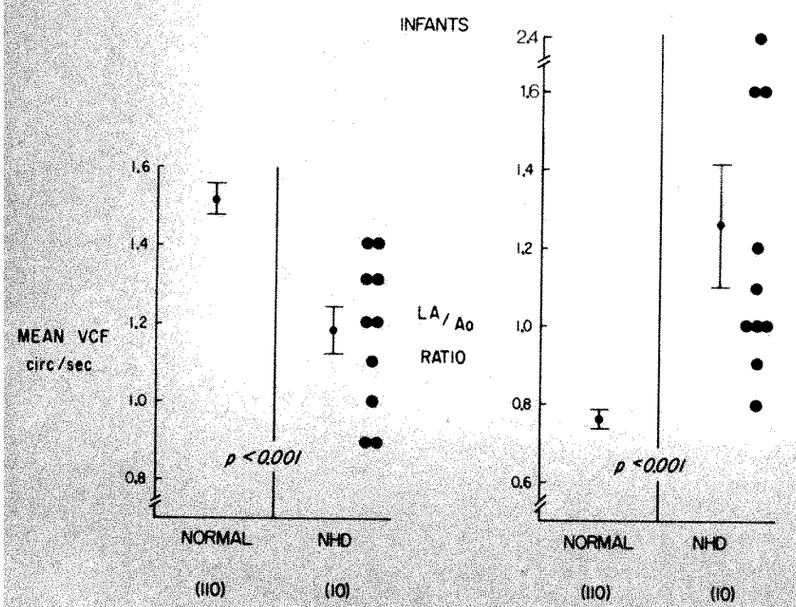

FIGURE 5. Mean Vcf and LA/Ao ratio data from normal infants and infants with nonstructural heart disease (NHD). Individual values for the infants with nonstructural heart disease are shown on the right of each column. The highest and lowest values for mean Vcf and LA/Ao ratio obtained in the normal infants are the same as those in the legends for Figures 2 and 3, respectively. Symbols and abbreviations as in Figure 4.

significant scatter, the mean LA/Ao ratio (1.26 ± 0.16) was significantly elevated (P <0.001).

Older Children

Normal values for mean Vcf and LA/Ao ratio in 45 older children (aged 2 to 10 years) were 1.34 ± 0.03 and 0.94 ± 0.02, respectively. No previous normal data exist for these variables in older children. Mean Vcf was significantly lower and the LA/Ao ratio significantly higher when compared with values in normal infants (P <0.001). However, no correlation was found between either of these echocardiographic indexes and age or body surface area.

When compared with normal children, seven patients with a clinical diagnosis of myocarditis or cardiomyopathy who had not yet received cardiac medications had a significantly lower mean Vcf (1.08 ± 0.07) and (although there was a significant range in individual patient data), a higher mean LA/Ao ratio (1.22 ± 0.26) (P <0.005) (Fig. 6).

Digitalis

To evaluate the ability of digitalis to alter acutely mean Vcf, 11 patients with the diagnoses shown in Figure 7 received a total dose of 35 to 45 μg/kg of digoxin

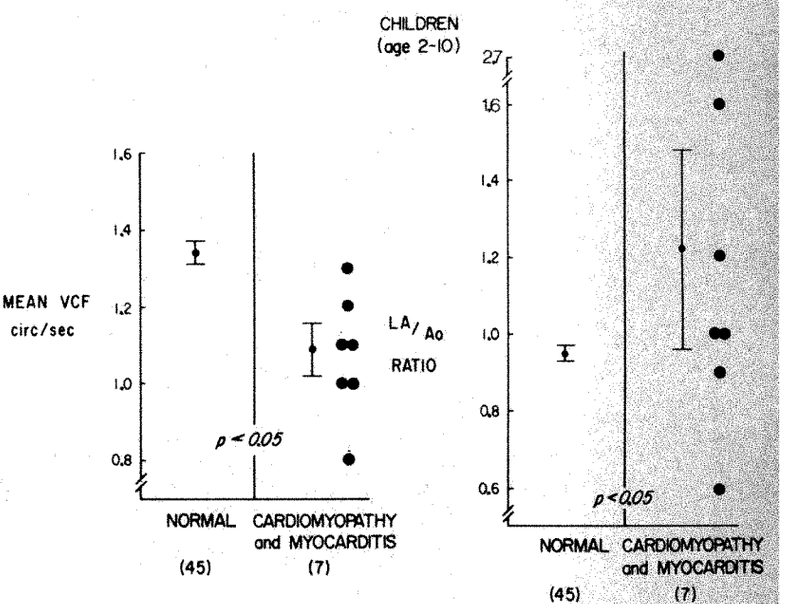

FIGURE 6. Mean Vcf and LA/Ao ratio data from normal children aged 2 to 10 years, and children with cardiomyopathy or myocarditis. The highest and lowest mean Vcf values encountered in the normal children were, respectively, 1.9 and 1.1 circumferences/sec, each in one child. The highest and lowest LA/Ao ratios encountered in the normal children were, respectively, 1.2 and 0.6, each in one child. Symbols and abbreviations as in Figure 4.

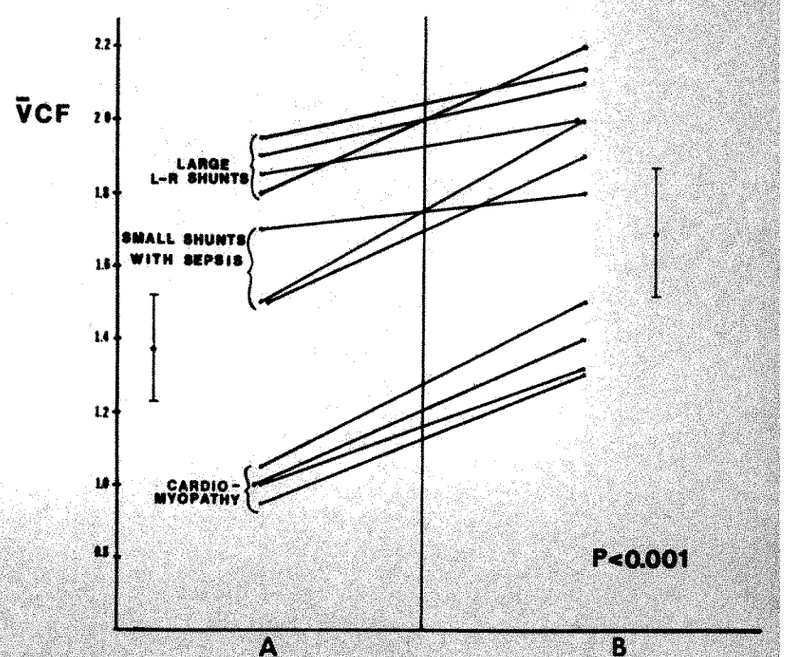

FIGURE 7. Serial determinations of mean Vcf in 11 patients who were digitalized over a 24 hour period and were studied echocardiographically 6 to 12 hours thereafter. Each **point** and the **vertical bars** represent the mean ± standard error for the total group. **A,** before digoxin. **B,** during digoxin maintenance therapy.

orally over a 24 hour period and underwent echocardiographic study 6 to 12 hours thereafter. Mean Vcf increased in each patient and the group average increased significantly (1.38 ± 0.07 to 1.69 ± 0.08, $P < 0.001$). The greatest increases were observed in the patients with cardiomyopathy, which had the lowest values before administration of digitalis.

Discussion

Experience with single crystal echocardiography has shown that difficulties in spatial orientation and angular errors in studying left ventricular dimensions in the small heart may lead to prohibitively large errors in cardiac volume calculations. Preliminary reports have suggested that left ventricular end-diastolic and left atrial dimensions determined by ultrasound may assist in the management of infants with a large left to right shunt.[7] However, absolute left ventricular dimension data may be unreliable because of the wide variability in these values in normal infants and children of the same weight.[4] Since mean velocity of circumferential fiber shortening (Vcf) is normalized for end-diastolic diameter, it is less sensitive to minor dimensional discrepancies. Values for mean Vcf obtained from slightly different areas of the mid-portion of the same ventricle were essentially identical despite variation in the absolute values for end-diastolic and end-systolic dimension obtained. Accordingly, to define more clearly clinical problems by characterizing patterns of cardiocirculatory dysfunction, we have employed an index of cardiac performance based on left ventricular fractional shortening from its end-diastolic dimension, that is, mean Vcf and the ratio of left atrial to aortic dimensions (LA/Ao ratio).

Ratio of left atrial to aortic dimension (LA/Ao): Left atrial volume is increased in the presence of intact atrial septum and left to right shunts distal to the systemic atrioventricular valves.[8,9] Although patients with a patent ductus arteriosus might be expected to have a greater aortic diameter than those with a ventricular septal defect, we found no important differences in LA/Ao ratio between these groups. Silverman et al.[10] have recently described elevated values of LA/Ao ratio in premature infants with patent ductus arteriosus and a substantial reduction in the ratio after surgical ligation. As in their study, we found little abnormality or serial variation in aortic diameter in any individual infant whose degree of left to right shunting altered significantly. As such, the LA/Ao ratio reflects alterations in left atrial size for a given infant. It is likely that such an approach for normalized examination of left atrial size compared with the aorta would not be useful in infants who have an abnormal aortic root, such as those with tetralogy of Fallot. Furthermore, our recent experience with biaxial left atrial dimensions using standard echocardiography from the anterior chest wall and suprasternal notch measurements of the superior-inferior left atrial dimension suggests that some infants with a large shunt may have "pancaking" of the left atrium so that standard echocardiography may underestimate left atrial size and therefore LA/Ao ratio.

Since left atrial volume and diameter may also change in response to changes in left ventricular performance, it is not surprising that we found high LA/Ao ratios in infants and older children with left ventricular dysfunction. Distinction between patient groups with shunt-induced elevations in LA/Ao ratio and impaired left ventricular myocardial function was achieved by analysis of mean Vcf data.

Mean velocity of circumferential fiber shortening (Vcf): Calculation of mean Vcf has proved to be a simplified measure for assessing left ventricular contractility in adults,[11–13] and preliminary angiographic data suggest that this index may also be of value in detecting children with impaired cardiac function.[14] In this study, this index appeared sufficiently sensitive in infants and children to separate patients with nonstructural heart disease from normal subjects even when these patients were receiving digitalis. Mean Vcf is increased in patients with a large left to right shunt even in the presence of cardiac decompensation because of both greater left ventricular filling and altered afterload. Left ventricular systolic wall tension may be reduced in patients with a ventricular septal defect since left ventricular emptying occurs at the onset of isovolumetric contraction. Further, in patients with a ventricular septal defect or patent ductus arteriosus, during systole there is runoff into a pulmonary vascular bed with relatively low resistance.

In this study, administration of digoxin to infants with a large shunt and to infants and children with nonstructural heart disease was associated with an increase in mean Vcf in each subject. Whereas this elevation was consistent, the magnitude of the digitalis-induced change did not appear large enough to account for the differences in Vcf between normal subjects and digitalis-treated infants with a large left to right shunt. Similarly, it would not appear likely that differences in mean Vcf among any of the groups could be accounted for by differences in heart rate.

Accuracy of echocardiographic data in infants and children: Some difficulties exist in applying the Vcf calculation in these infants and children. When ejection time is calculated from mitral valve echoes, no correction exists for that portion of the isovolumic contraction time included between mitral valve closure as determined by echocardiogram and the opening of the aortic valve. As in our previous report[5] of Vcf data in normal infants, no correction for isovolumic contraction time was applied since no reliable data exist for this determination in infants with various heart rates. External pulse carotid ejection times cannot be measured in small premature infants. Axillary arterial data have been reported for full-term neonates.[15] Nevertheless, questions may be raised as to how accurately these peripheral tracings reflect intracardiac events.

In selected cases in this study, aortic valve echo visualization was sufficiently precise for the calculation of preejection period and ejection time. These data were compared at comparable electrocardiographic R-R intervals with the method employing the mitral valve echoes for timing. The results indicate that the over-

estimation of ejection time measured by the mitral valve technique is 5 ± 0.4 percent in normal subjects. The error introduced in ejection time was negligible in the group with a large shunt and was 10 ± 1.3 percent in the group with cardiomyopathy. In the infants with nonstructural heart disease and the children with cardiomyopathy, an overestimation of ejection time by this method would be expected to lower proportionately the Vcf values reported. However, and of key importance, when the results from the normal infants versus infants with cardiomyopathy, and from the normal children versus children with cardiomyopathy, were adjusted for maximal predicted error and compared the data were still statistically separable ($P < 0.001$). Of interest, in a small subsequently studied group of children with cardiomyopathy and normal children individually matched for age and heart rate, accurate correction for preejection period was available. The ejection times were calculated from aortic valve tracings matched for R-R interval with portions of the record from which left ventricular end-diastolic and end-systolic dimension were measured. No significant differences in ejection time existed between the normal subjects and those with cardiomyopathy. Depressed left ventricular function was equally detectable with the value for mean Vcf and with the normalized fractional shortening ratio of left ventricular diameters.* Such an approach has not yet been completed in other study groups.

$$*\Delta D = \frac{\text{left ventricular end-diastolic dimension (mm)} - \text{end-systolic dimension (mm)}}{\text{end-diastolic dimension (mm)}}$$

Clinical implications: The major finding of this study is that the combination of the two echocardiographically derived measurements, mean Vcf and LA/Ao ratio, allowed a distinction between a normal patient group, a group with nonstructural heart disease and groups with a left to right shunt through a ventricular septal defect or patent ductus arteriosus. In the group with a large shunt, both ultrasonic values are abnormally high. In the group with cardiomyopathy, myocarditis or metabolic heart disease, a reduction in mean Vcf accompanies a substantial increase in the LA/Ao ratio. In infants, the respiratory and cardiac signs and symptoms arising from structural cardiac disease are often difficult to distinguish from those associated with primary pulmonary or metabolic disorders.[16] The systematic utilization of such reproducible noninvasive ultrasonic measurements may facilitate clinical evaluation.

Serial determination of mean velocity of circumferential fiber shortening and ratio of left atrial to aortic root diameter in the same patient has proved of special worth. In particular, we have often employed the two measurements to gauge serially the changing hemodynamics in the small premature infant with both the respiratory distress syndrome and a ductus arteriosus in whom changing patency and pulmonary vascular bed dynamics frequently alter the magnitude of shunting.

Echocardiographic studies are without known risk and their incorporation into the routine of clinical care allows a more systematic approach to the planning and testing of effects of therapeutic interventions in critically ill newborns.

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Echocardiographic Manifestations of Single Ventricle

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Eight patients with single ventricle were studied echocardiographically. In six, the ventricular septum was not detectable; in two, a septal-like bulboventricular ridge was identified. Two atrioventricular (A-V) valves were found in all patients; in six, both valves were identified simultaneously with the transducer held stationary along the left sternal edge. Dextrotransposition of the great arteries was noted in three patients. The echocardiogram of one of four patients with levotransposition of the great arteries was consistent with later proved left A-V valve stenosis associated with Ebstein's malformation. Mitral-semilunar valve continuity was present in five cases. Echocardiographically, the absence of the ventricular septum in a patient with two A-V valves makes a diagnosis of single ventricle likely. The presence of ventricular septal-like echoes does not exclude the diagnosis of single ventricle since the right ventricular infundibulum may remain as a small outlet chamber separated from the left ventricle by an eccentric bulboventricular ridge.

Echocardiography is a useful tool in evaluating cardiac anatomy in the patient with congenital heart disease.[1–3] Since echocardiographic data in cases of single ventricle are limited,[4,5] we have used cardiac ultrasound to evaluate eight patients with this defect. Specifically sought were: (1) the absence or presence of the ventricular septum; (2) the identification and motion pattern of both atrioventricular (A-V) valves; and (3) the relation of the bulboventricular ridge, if identified, to the two A-V valves.

Material and Methods

The diagnosis of single ventricle with two atrioventricular valves was made in eight patients, aged 1 month to 22 years (Table I). The diagnosis was established at cardiac catheterization and angiocardiography and confirmed at open heart surgery in two patients. Four of the patients with single ventricle had levotransposition of the great arteries, three had dextrotransposition of the great arteries, and one had normally related great arteries. All patients had normal cardiac and visceral situs; no splenic anomalies were present.

Echocardiographic examination was performed with a Unirad C-100 echograph combined with an Electronics for Medicine strip chart recorder. A 2.0 megahertz nonfocused transducer with an outer diameter of 0.5 inch (1.27 cm) was used in the younger patients and a 3.5 megahertz transducer with an outer diameter of 0.6 inch (1.52 cm) focused at 7.5 cm in the older patients. All patients were examined in both the supine and left lateral positions with the transducer placed in the third or fourth intercostal space along the left sternal border. With the transducer in this position, the ultrasonic beam was directed so as to record the mitral and tricuspid valves, the great arteries and the ventricular cavity (Fig. 1).

Results

Six of eight patients had absence of the ventricular septum by echocardiography (Fig. 2). In two patients (Cases 4 and 8), a bulboventricular

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TABLE I

Echocardiographic and Angiographic Data in Eight Cases

Case no.	Age (yr) & sex	Echocardiographic Findings			Angiocardiographic Findings	
		Mitral-Semilunar Valve Continuity	Bulboventricular Ridge (Outlet Chamber)	2 A-V Valves	Great Arteries	Outlet Chamber
1	3.5F	Yes	No	Transducer stationary	D-TGA	No
2	8M	Yes	No	Transducer stationary	D-TGA, PS	Yes
3	12M	Yes	No	Transducer stationary	L-TGA, PS	Yes
4	20F	No	Yes	Transducer moved	D-TGA, PS	Yes
5	21M	Yes	No	Transducer stationary	L-TGA	No
6	1F	Uncertain	No	Transducer stationary	Normal	Yes
7	9/12F	No	No	Transducer stationary	L-TGA	No
8	7M	Yes	Yes	Transducer moved	L-TGA	Yes

A-V = atrioventricular; D = dextro; L = levo; PS = pulmonary stenosis; TGA = transposition of the great arteries.

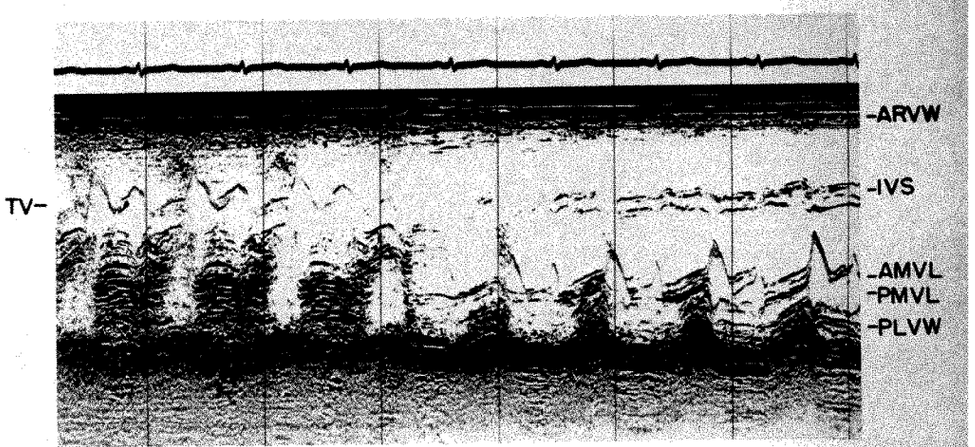

FIGURE 1. Echocardiogram of a patient with a small ventricular septal defect showing the usual relation of the right and left atrioventricular (A-V) valves obtained by rotating the transducer laterally from the tricuspid valve to the mitral valve position. The ventricular septum is interposed between the A-V valves. AMVL = anterior mitral valve leaflet; ARVW = anterior right ventricular wall; IVS = interventricular septum; PLVW = posterior left ventricular wall; PMVL = posterior mitral valve leaflet; TV = tricuspid valve.

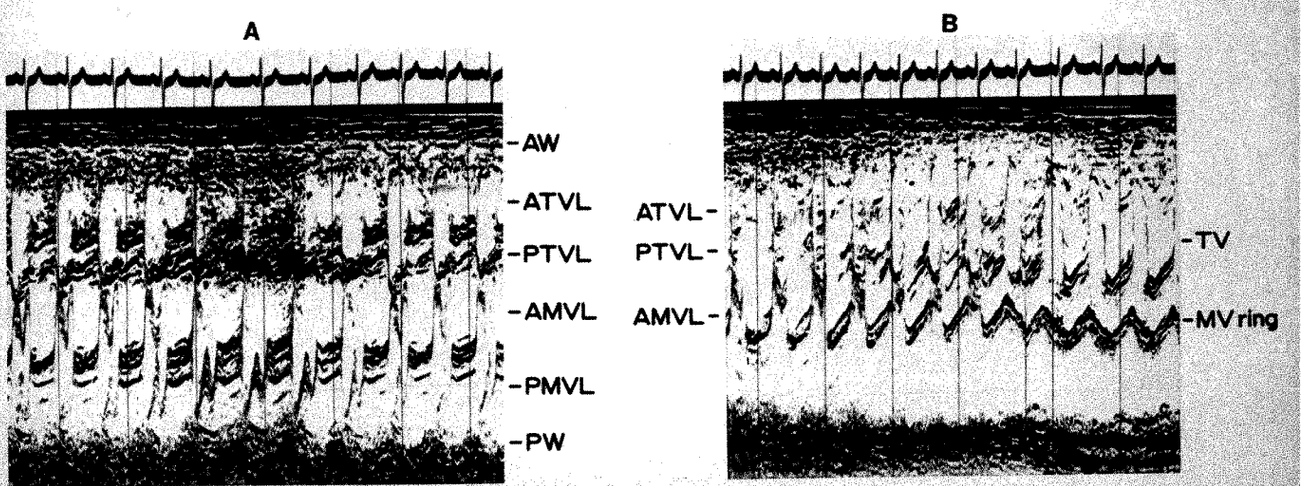

FIGURE 2. Case 2. Echocardiogram from an 8 year old boy with single ventricle. **A,** the transducer is stationary; two A-V valves are contiguous without an intervening ventricular septum. There is apposition of the basal aspect of the septal leaflet of the tricuspid valve to the anterior leaflet of the mitral valve. **B,** the transducer is rotated cephalad and the mitral valve echo becomes the mitral valve ring. Note that only one ventricular cavity is identified. ATVL = anterior tricuspid valve leaflet; AW = anterior wall; MV = mitral valve; PTVL = posterior tricuspid valve leaflet; PW = posterior wall; other abbreviations as in Figure 1.

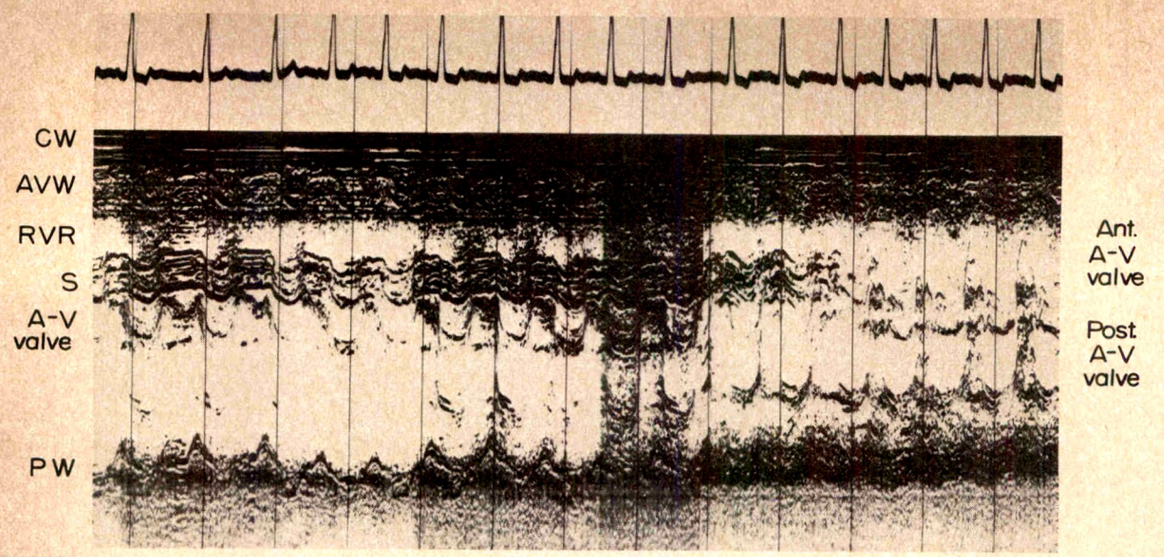

FIGURE 3. Case 4. The echocardiogram of a 20 year old woman with single ventricle (type A) and dextrotransposition of the great arteries, showing a bulboventricular ridge, anteriorly resembling a ventricular septal echo. The small infundibular cavity or right ventricular remnant (RVR) is anterior to the bulboventricular ridge. The posterior A-V valve is beneath or posterior to the ridge; the anterior A-V valve straddles the rim of the bulboventricular ridge as the sweep progresses. Ant. = anterior; AVW = anterior ventricular wall; CW = chest wall; Post. = posterior; other abbreviations as in Figures 1 and 2.

ridge was identified (Fig. 3). In six patients, both atrioventricular valves were identified simultaneously with the transducer held stationary along the left sternal border. In these cases the right A-V valve was directly anterior to the left A-V valve (Fig. 2 and 4). In the other two patients (Cases 4 and 8), the two A-V valves were located separately by variation of transducer position (Fig. 3). Continuity between the left A-V valve and a semilunar valve was demonstrated in five cases (Fig. 5) and discontinuity or uncertain continuity in three.

In two of the eight patients, the bulboventricular ridge was identified (Fig. 3), separating a small anterior outlet chamber (right ventricular infundibulum) from the large left ventricular chamber. The eccentrically placed bulboventricular ridge was located by angling the transducer sagittally across the chest; the conventional transducer position eliminated this echo.

Discussion

Single ventricle in this study is defined as a large functional ventricle or sinus that receives both the mitral and tricuspid valves; a rudimentary outflow chamber is usually present. In no case was the sinus portion of the right ventricle present. This definition excludes anomalies with a dominant ventricle and absence of an atrioventricular valve (for example, mitral or tricuspid atresia). None of our patients had a common A-V valve. Although a common A-V valve occurred in one third of the cases of single ventricle studied at autopsy by Van Praagh et al.[6] and in six of seven cases studied by echocardiography by Chesler et al.,[4] Marin-Garcia et al.[7] did not include cases with common A-V valve in their angiographically and autopsy-proved cases of single ventricle.

The presence of both A-V valves recorded simultaneously without an intervening ventricular septum was the commonest echocardiographic finding in our patients with single ventricle (Fig. 2 and 4). However, the presence of a bulboventricular ridge may also be noted and does not exclude the diagnosis of single ventricle (Fig. 5). The right ventricular infundibulum may remain as a small discrete chamber bounded by a shelf-like bulboventricular ridge. Thus, at angiography, an anatomically discrete small infundibular chamber is a frequent hallmark of single ventricle, occurring in 79 percent of an autopsy series studied by Van Praagh et al.[8]

Mitral-semilunar valve continuity: The echocardiographic finding of superimposition of the great arteries may be present, since 85 percent of patients with single ventricle have dextro- or levotransposition in equal numbers.[6] Continuity between the mitral valve and the pulmonary valve is not uniformly present. In 57 patients with single ventricle and two A-V valves and either dextro- or levotransposition of the great arteries, mitral-semilunar continuity was demonstrated angiographically and pathologically in 49 patients, but continuity was not present in 8 patients with a double conus whose aorta and pulmonary artery lay in the same frontal plane.[9] In patients with single ventricle and normally positioned great arteries, mitral-aortic valve continuity was consistently found. In our eight patients, seven of whom had dextro- or levotransposition of the great arteries, five had mitral-semilunar valve continuity. On the other hand, consistent mitral-pulmonary arterial discontinuity by echocardiography in patients with single ventricle has been described.[5]

Differentiation from levotransposition with septum present: Clinically, single ventricle with or without pulmonary stenosis may mimic cyanotic conditions presenting with decreased pulmonary blood flow (tetralogy of Fallot and tricuspid atresia) or with in-

creased pulmonary blood flow (transposition of the great arteries, truncus arteriosus and double outlet right ventricle with pulmonary stenosis). These cardiac defects may be separated by echocardiography. Thus, the echocardiographic absence of the ventricular septum in a patient with two A-V valves and transposition of the great arteries, or finding the ventricular septum anterior to two A-V valves in association with transposition of the great arteries virtually confirms the diagnosis of single ventricle. Difficulty may arise, however, in distinguishing single ventricle with two A-V valves from: (1) levotransposition of the great arteries with a well developed ventricular septum; and (2) complete A-V canal. In levotransposition, the septum lies perpendicular to the frontal plane and is thus difficult to demonstrate echocardiographically utilizing a conventional parasternal transducer position. We have demonstrated the ventricular septum in four consecutive cases of levotransposition by placing the transducer at the cardiac apex. The transducer positioned at the third left intercostal space pointing posteromedially located the ventricular septum in another case.

Differentiation from complete A-V canal: In patients with complete A-V canal, the interventricular septum may not appear in the echocardiographic position that demonstrates the A-V valves. A recent echocardiographic study demonstrated a large single A-V valve consistently.[10] In half of the patients, the valve's common anterior leaflets and its mitral and tricuspid halves occupied a central systolic position between the two ventricles, moving apart in diastole; the ventricular septum was not identified between the leaflets. In the other half of the patients, the common anterior A-V valve leaflet moved from the left ventricle in systole into the right ventricle in diastole in a large excursion. In addition, mitral-aortic continuity was consistently demonstrated. The great arteries were in normal position in complete A-V canal since transposition of the great arteries is uncommonly associated with this malformation. Single ventricle with a common A-V valve would be difficult to differentiate from complete A-V canal. However, the presence of transposition of the great arteries in a patient without echocardiographic

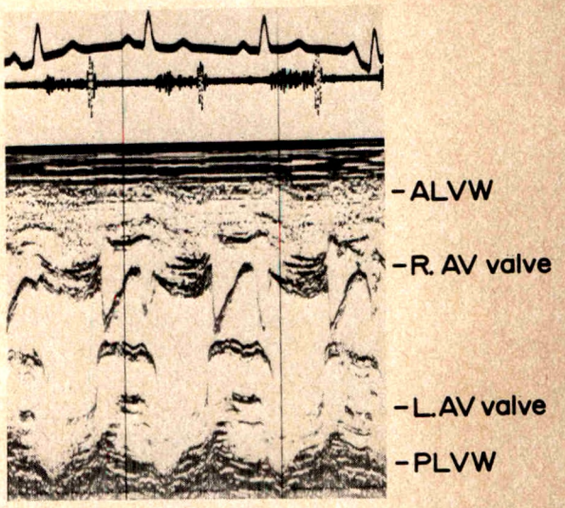

FIGURE 4. Case 3. Echocardiogram of a 12 year old boy with single ventricle, levotransposition of the great arteries and Ebstein's anomaly of the left A-V valve. The latter is distinctly stenotic showing a decreased diastolic slope, no A point and anterior movement of the posterior leaflet. There is delayed closure of this valve compared with the right A-V valve, suggesting Ebstein's anomaly. Both A-V valves open into a large left ventricle; no intervening ventricular septum is noted. Cardiac catheterization confirmed the diagnosis of single ventricle with levotransposition of the great arteries and slightly incompetent left A-V valve with an Ebstein-like malformation. At surgery, the additional diagnosis of stenosis of the left A-V valve was verified; the left atrial pressure measured 25 cm water. ALVW = anterior left ventricular wall; AV = atrioventricular; L. = left; PLVW = posterior left ventricular wall; R. = right.

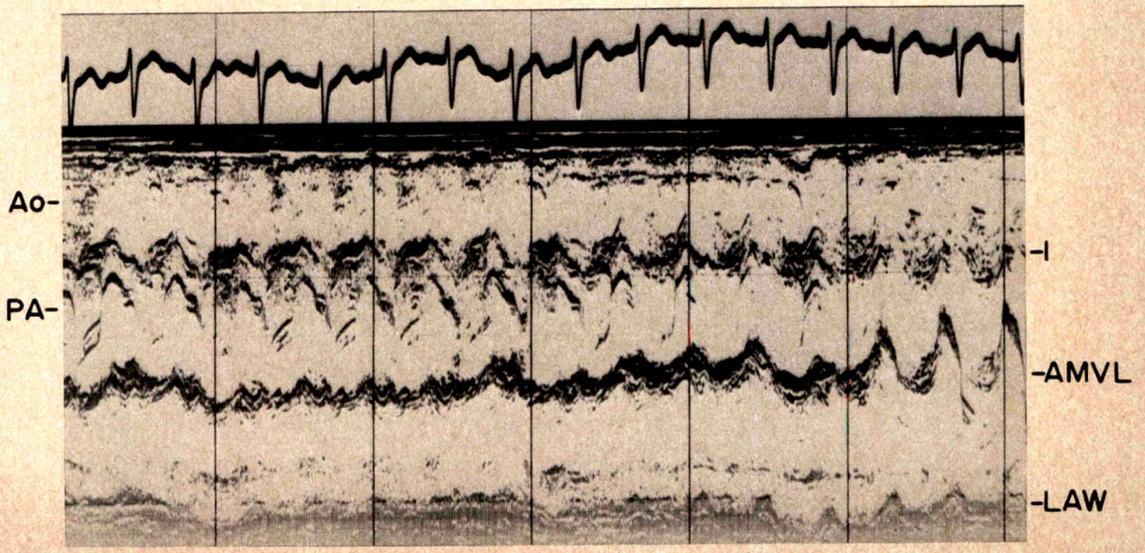

FIGURE 5. Case 1. Echocardiogram recorded at the level of the great arteries of a 3 year old girl with single ventricle and dextrotransposition of the great arteries at autopsy. The aorta (the smaller great vessel) is anterior to the pulmonary artery (the great vessel of larger diameter). Continuity between the anterior mitral valve leaflet and the pulmonary artery is noted. Conal tissue extends between the great arteries into the left ventricle. AMVL = anterior mitral valve leaflet; Ao = aorta; I = conal tissue; LAW = left atrial wall; PA = pulmonary artery.

demonstration of the ventricular septum would favor the diagnosis of single ventricle.

Differentiation from tricuspid or mitral atresia: It may be necessary to differentiate single ventricle with a common A-V valve from tricuspid and mitral atresia. In our cases of tricuspid valve atresia, the tricuspid valve echo could not be found, a small anterior right ventricular chamber could always be identified, and mitral valve-semilunar valve continuity was consistently present. A large right ventricular cavity, absence of the mitral valve echo, and a small or absent left ventricular chamber occurs in patients with mitral atresia. Patients with a single ventricle and a common A-V valve show a wide-ranging anterior or anterior and posterior leaflet echo of the single valve with absent septal echoes.

Overriding of tricuspid valve: Two A-V valves with no intervening septum and straddling or overriding of the tricuspid valve in relation to the ventricular septum have been defined by echocardiography in patients with double inlet left ventricle.[11] Case 4 (Fig. 3) demonstrates overriding of the anterior A-V valve over the bulboventricular ridge; the angiogram showed common ventricle with an outflow chamber (type A).

Left A-V valve stenosis: The association of congenital left A-V valve stenosis and single ventricle occurred in 12 percent of one series of cases.[6] In Case 3, with levotransposition of the great arteries and single ventricle, echocardiography was useful in detecting left A-V valve stenosis associated with mild mitral incompetence and Ebstein's malformation (Fig. 4).

Clinical application: Since single ventricle may be difficult to assess completely even after selective angiography, cardiac ultrasound may be of considerable help in defining the presence or absence of the ventricular septum, the position of the bulboventricular ridge relative to the A-V valves and the ventricular cavity, and whether two A-V valves are present and whether A-V valve stenosis or prolapse is demonstrated. These data are particularly important to the cardiovascular surgeon who is considering the repair of single ventricle.[12–14]

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Double Outlet Right Ventricle: Hemodynamic and Anatomic Correlations

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There are 16 possible variations of double outlet right ventricle with regard to interrelations of the great arteries and to location of the ventricular septal defect. In a series of 62 cases, approximately two thirds of patients had the great arteries in a side by side relation, and most (28 of 41) had the ventricular septal defect in a subaortic position. In double outlet right ventricle with malposition of the great arteries, the ventricular septal defect was either subpulmonary or subaortic. Four of the 13 patients with subpulmonary ventricular septal defect had a supracristal defect with side by side relation of the great arteries (Taussig-Bing anomaly), and 9 patients had malposition of the great arteries with an infracristal ventricular septal defect. In all patients with subpulmonary ventricular septal defect, pulmonary arterial oxygen saturation was greater than systemic arterial saturation regardless of the relation of the great arteries.

Forty patients had subaortic ventricular septal defect. In 24 of these patients, including 7 with malposition of the great arteries, systemic arterial oxygen saturation was greater than pulmonary arterial saturation. However, in 9 patients (25 percent) the reverse was true, as seen in complete transposition of the great arteries and in Taussig-Bing anomaly. Thus, pulmonary arterial oxygen saturation greater than systemic arterial saturation is not reliable evidence of a Taussig-Bing anomaly. Of the 25 patients with such saturation, only 4 had the Taussig-Bing anomaly.

In recent years, progress in corrective surgery of complex congenital heart disease has been possible, in part because of a better understanding of the pathologic anatomic features and increased ability to make the exact diagnosis by cardiac catheterization and selective angiocardiography. The management currently employed for the various types of double outlet right ventricle is a clear example of such progress.

In 1949, Taussig and Bing[1] first described a patient whose transposed aorta originated from the right ventricle whereas the pulmonary artery arose from the right ventricle and partially overrode the ventricular septum. This condition is now considered the Taussig-Bing type of double outlet right ventricle.

In 1957, Witham[2] first applied the term double outlet right ventricle to a condition considered a partial transposition complex in which both great arteries arose from the right ventricle. He summarized six reported cases and added four cases of his own, dividing them into two groups, the "Fallot" type and the "Eisenmenger" type, depending on, respectively, the presence or absence of pulmonary stenosis.

In 1961, Neufeld et al.[3,4] reported 14 cases, and in 1962 they[5] added another series of 10 cases. They classified double outlet right ventricle not associated with pulmonary stenosis on the basis of relation of the great vessels or position of the ventricular septal defect.

In 1972, Lev et al.[6] emphasized the variations in location of the ventricular septal defect in relation to the great arteries. Later, Zamora et al.[7] studied the specimens from 33 autopsy cases of double outlet right

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ventricle and also classified them into five types on the basis of position of the ventricular septal defect.

In 1968, Patrick and McGoon[8] proposed a surgical classification of the various types of double outlet right ventricle according to location of ventricular septal defect and relation of great arteries, excluding the presence or absence of pulmonary stenosis.

In 1965, Carey and Edwards[9] first reported the angiocardiographic features of double outlet right ventricle. They emphasized the following diagnostic criteria: opacification of both great arteries from the right ventricle, visualization of the aortic and pulmonary valves in the same horizontal plane, frequent malposition of the aorta in the lateral view and, in the frontal view, a "tongue-like" filling defect at the base of the right ventricle that represents the parietal limb of the crista supraventricularis and forms a division for two outflow tracts. In 1970, Hallermann et al.[10] studied the angiocardiographic and anatomic findings in 42 cases of double outlet right ventricle. They recognized the criteria proposed by Carey and Edwards[9] and considered that, in the lateral view, the mitral valve was not in continuity with either semilunar valve.

In the hemodynamic classification of Neufeld et al.,[3–5] double outlet right ventricle was categorized into two major groups, depending on the presence or absence of pulmonary stenosis. In the presence of pulmonary stenosis, the hemodynamic features closely resembled those of tetralogy of Fallot. In patients without pulmonary stenosis, the hemodynamic findings resembled those in patients who have a large ventricular septal defect and a dominant left to right shunt or who have a right to left shunt and pulmonary vascular obstructive disease. Neufeld et al. suggested that the position of the ventricular septal defect was a significant factor determining intracardiac streaming. In 1967, Hazell et al.,[11] reviewing 25 cases of double outlet right ventricle, noted that the hemodynamic findings were similar to those described by Neufeld et al.

Aim of the Study

We reviewed the Mayo Clinic experience with a large series of patients with confirmed double outlet right ventricle and complete hemodynamic and angiocardiographic data in order to delineate the relative importance to hemodynamic status of certain anatomic features. These features included relation of the great arteries, presence or absence of pulmonary stenosis, location of the ventricular septal defect and presence or absence of significant pulmonary vascular obstructive disease.

Definition of Terms

Relation of the great arteries: There are four types of relation between the great arteries at the level of the semilunar valves: (1) Normal relation. The pulmonary arterial trunk is anterior and to the left of the aorta. (2) Side by side relation. The aorta is to the right of the pulmonary artery, and the semilunar valves lie in approximately the same transverse plane. This is the classic interrelation of the great arteries in double outlet right ventricle. (3) Dextromalposition of the great arteries. The aorta is to the right of and anterior to the pulmonary artery. (4) Levomalposition. The aorta is to the left of and anterior to the pulmonary artery.[12]

Position of the ventricular septal defect: There are four types of ventricular septal defect in double outlet right ventricle: (1) The subaortic type, characterized by a ventricular septal defect that is related more closely to the aortic valve than to the pulmonary valve. (2) The subpulmonary type, in which the ventricular septal defect is closely related to the pulmonary valve. The defect is located above the septal limb of the crista supraventricularis. The subpulmonary type, together with double outlet right ventricle, is considered synonymous with the Taussig-Bing complex. (3) The subaortic and subpulmonary type, in which the ventricular septal defect is closely related to both semilunar valves. The defect is separated from these valves by being centered below a muscular flange and below the crista supraventricularis. (4) The remote type, in which the ventricular septal defect is distant from both semilunar valves.

Double outlet right ventricle: The condition in which both great arteries originate from the right ventricle, also known as double outlet right ventricle, has been defined differently by different workers. Neufeld et al.[3–5] defined it essentially as follows: Both great arterial trunks (the aorta and pulmonary trunk) arise exclusively from the morphologic right ventricle. Neither semilunar valve is in fibrous continuity with either atrioventricular valve. Usually, a ventricular septal defect is present and represents the only outlet for the left ventricle. Pulmonary or subpulmonary stenosis may be present or absent. Lev's group[6] adopted a less rigid definition. They indicated that both arterial trunks emerge completely or almost completely from the right ventricle and there may or may not be mitral-aortic or mitral-pulmonary continuity. In our study, when cases fulfilled the Neufeld definition they were grouped as classic examples of double outlet right ventricle. When both great vessels arose above the right ventricle but fibrous continuity between the aortic and mitral valves was present, the cases were excluded.

Materials and Methods

From 1960 to 1974, 88 patients with double outlet right ventricle were seen at the Mayo Clinic (86 with ventricular septal defect and 2 with intact ventricular septum). The 16 patients with isolated dextrocardia or levocardia or total situs inversus (2 patients) were excluded. Seventy-two patients exhibited levocardia and normal orientation of the cardiac chambers. Of the 72 patients, 62 had available complete hemodynamic data, including pulmonary arterial and systemic arterial oxygen saturation levels and pressures. The age range of these 62 patients was 1 month to 33 years, with a mean of 7.5 years. The distribution of patients according to sex was equal.

The anatomy of the double outlet right ventricle and the location of the ventricular septal defect were determined in these 62 cases, in 39 cases by operative observation only, in 13 cases by autopsy and operative observation, in 3 by autopsy only and in 7 by angiocardiographic findings only.

Cardiac catheterization was performed by standard methods previously reported.[13,14] When possible, the pulmonary arterial, mixed venous and systemic arterial blood samples were drawn simultaneously by a double venous catheter technique. When only one venous catheter was used, the samples were taken in rapid succession from several locations. Systemic and pulmonary blood flow values were calculated with use of the Fick principle. The total pulmonary resistance and systemic resistance were expressed as units m^2.

The position of the ventricular septal defect was defined in relation to the great arteries. Thus, the defects were (1) subpulmonary, (2) subaortic, (3) subaortic and subpulmonary, and (4) remote from each semilunar valve. In three cases in which the defect was remote, the defect was part of a persistent common atrioventricular canal. Two patients in our series had no ventricular septal defect.

Histologic examination of the pulmonary vascular bed was made in all autopsy cases in which there was no pulmonary stenosis and in cases with pulmonary stenosis in which an anastomotic procedure had been performed. The pulmonary vascular changes were graded according to the classification of Heath and Edwards.[15]

TABLE I

Relation of Great Arteries and Location of Ventricular Septal Defect in 60 Cases* of Double Outlet Right Ventricle

Great Vessel Relation	Location of Ventricular Septal Defect				
	Subpulmonary	Subaortic	Subaortic and Subpulmonary	Remote	Total
Normal	0 (0†)	2 (0)	0 (0)	0 (0)	2 (0)
Side by side	4 (0)	28 (14)	2 (0)	5 (2)	39 (16)
Dextro-malposition	6 (3)	9 (7)	0 (0)	0 (0)	15 (10)
Levo-malposition	3 (2)	1 (1)	0 (0)	0 (0)	4 (3)
Total	13 (5)	40 (22)	2 (0)	5 (2)	60 (29)

*There were two additional cases with intact ventricular septum; each showed malposition of the great arteries without pulmonary stenosis (one dextro and one levo).

†Numbers in parentheses represent patients with pulmonary stenosis.

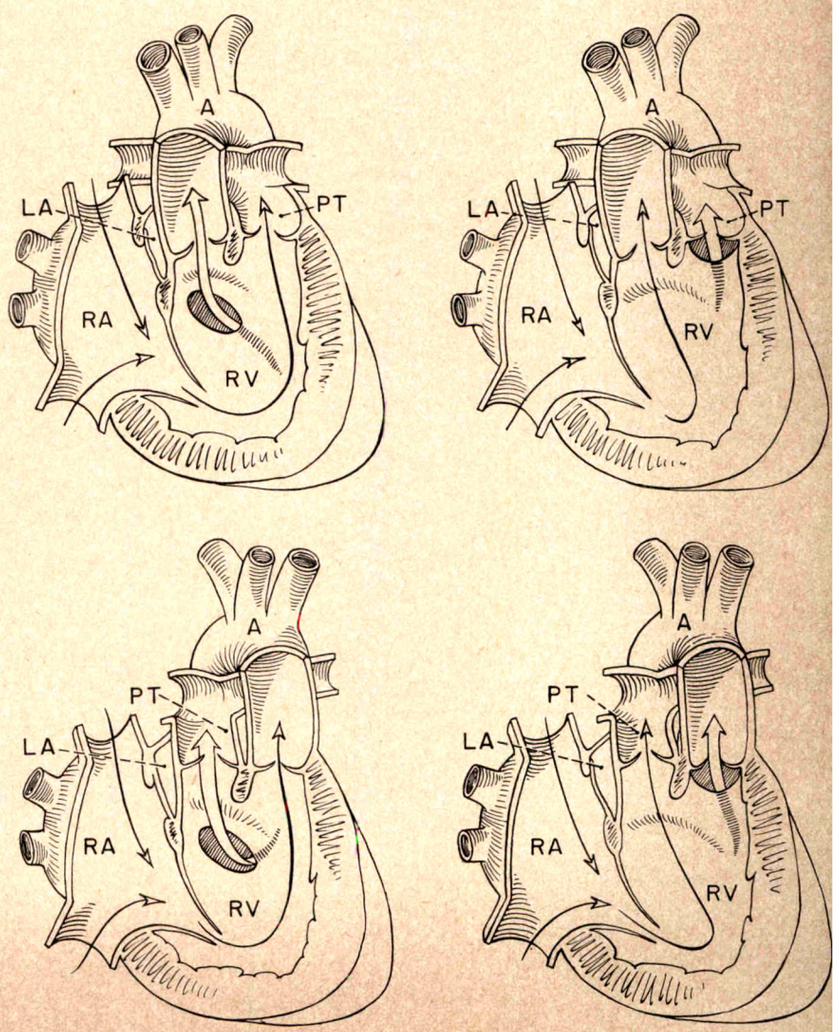

FIGURE 1. Top left and right, double outlet right ventricle with side by side relation of the great arteries. **Top left,** ventricular septal defect below the septal limb of the crista supraventricularis in subaortic position. Delivery of left ventricular blood to the aorta (A) is favored. **Top right,** ventricular septal defect above the septal limb of the crista. Streaming favors delivery of left ventricular blood to the pulmonary trunk (PT). (From Neufeld et al.[5] with permission.) **Bottom left and right,** double outlet right ventricle with malposition of great arteries, illustrating that, for a particular location of ventricular septal defect, streaming depends on nearness of a particular great artery to the defect. **Bottom left,** defect below the septal limb of the crista. The defect is more closely related to the pulmonary trunk than to the aorta, thus favoring delivery of left ventricular blood to the pulmonary trunk, in contrast to the situation shown at **top left. Bottom right,** ventricular septal defect lies above the septal limb of the crista. It is closely aligned with the malpositioned aorta, thus favoring delivery of left ventricular blood to the aorta, in contrast to the situation shown at **top right,** wherein the great arteries are in a side by side relation. LA = left atrium; RA = right atrium; RV = right ventricle.

TABLE II

Associated Cardiovascular Anomalies in 62 Cases of Double Outlet Right Ventricle

Anomalies	Case no.	Total
Pulmonary stenosis	1 through 29	29
Atrial septal defect	2, 6, 11, 16, 18, 23, 24, 28, 37, 48, 49, 53, 54, 56, 57, 62	16
Patent ductus arteriosus	24, 32, 40, 44, 45, 52, 54, 55, 56, 60	10
A-V canal (remote ventricular septal defect)	17*, 18, 47, 49, 57†	5
Anomalous coronary artery	11, 12, 16, 24, 28	5
Additional muscular ventricular septal defect	7, 28, 47	3
Subaortic stenosis	9, 15	2
Parachute mitral valve	26, 48	2
Intact ventricular septum	48, 62	2
Obstructive ventricular septal defect	26	1
Mitral atresia	62	1
Coarctation of aorta	52	1

*VSD atrioventricular canal type.
†Straddling mitral valve.

Biplane roll film angiocardiograms were available in 47 of the 62 cases and were studied with particular emphasis on the interrelation of the great arteries and the position of the ventricular septal defect with respect to the great arteries.

Cases were classified according to the presence or absence of pulmonary stenosis. The group without pulmonary stenosis was subclassified into those with and without pulmonary vascular obstructive disease. Pulmonary vascular obstructive disease was considered present either when the calculated total pulmonary resistance was 9 units m^2 or greater[16] or when the histologic classification of pulmonary vascular disease was grade 3 or greater.[15]

From the hemodynamic data, three patterns of arterial oxygen saturation were observed: (1) pulmonary arterial saturation greater than systemic arterial saturation (PA >SA), (2) systemic arterial saturation greater than pulmonary arterial saturation (SA >PA), and (3) pulmonary arterial saturation equal to systemic arterial saturation (PA = SA). A difference of less than 2 percent was considered significant when simultaneous systemic and pulmonary arterial samples were obtained.

Results

Anatomic Observations

The relation of the great arteries was as follows: side by side (39 cases), dextromalposition (16 cases), levomalposition (5 cases) and normal (2 cases). Of the 62 patients, 60 had a ventricular septal defect and 2 had an intact ventricular septum, each of the latter with malposition of the great arteries (one dextro and one levo). Among the 60 patients with ventricular septal defect, the defect was large in 59 and obstructive in 1 (case 26). The position of the defect with respect to the origins of the great arteries, in order of decreasing frequency, was as follows: subaortic (40 cases), subpulmonary (13 cases), remote (5 cases) and subaortic and subpulmonary (2 cases) (Table I).

For a given part of the ventricular septum containing a defect, the relation of the defect to the great arteries varied with the position of the great arteries. When the great arteries were in a side by side relation, an associated subpulmonary ventricular septal defect lay above the septal limb of the crista supraventricularis. If the same type of defect were associated with malposition of the great arteries, it lay in a subaortic position. Similarly, a subaortic defect associated with a side by side relation of the great arteries lay in an infracristal position. Such a defect would be subpulmonary if there were associated malposition of the great arteries (Fig. 1).

Location of ventricular septal defect and position of great arteries: The most frequent combination of location of ventricular septal defect and position of great arteries was the side by side relation of the great arteries with subaortic ventricular septal defect (28 of 60 patients, 47 percent) (Table I; Fig. 1, top left). The next most frequent combination was subaortic ventricular septal defect with malposition of the great arteries (Fig. 1, bottom right), found in 10 patients (9 with dextromalposition and 1 with levomalposition). This was followed in frequency by subpulmonary ventricular septal defect and malposition of the great arteries (six cases of dextromalposition and three of levomalposition) (Fig. 1, bottom left). In five patients, the ventricular septal defect was remote from the great arteries, which were in a side by side relation. The classic Taussig-Bing anomaly (subpulmonary ventricular septal defect and side by side relation of the great vessels) was seen in only four patients (Fig. 1, top right). The least common combinations were subaortic and subpulmonary ventricular septal defect with side by side relation of the great arteries (two patients) and subaortic ventricular septal defect and normally related great arteries (two patients).

Pulmonary stenosis: This was a frequently associated anomaly, being observed in 29 of the 62 patients (47 percent) (Tables II and III). This condition tended to be associated with dextromalposition or levomalposition of the great arteries, regardless of the position of the ventricular septal defect (13 of 19 patients, 68 percent). In the most common combination, the side by side relation of the great arteries associated with subaortic ventricular septal defect, pulmonary stenosis was noted in 14 of 28 patients (50 percent).

Pulmonary vascular disease: Classic obstructive pulmonary vascular disease was seen in patients without pulmonary stenosis. Of the 33 patients without pulmonary stenosis, 21 had pulmonary vascular obstructive disease as previously defined (Table IV). Two patients with mild pulmonary stenosis (Cases 7 and 9) had grade 3 or 4 hypertensive pulmonary vascular disease histologically (Table III). Among the patients without pulmonary stenosis were two 2 month old infants (Cases 59 and 62) (Table IV) with high levels of pulmonary vascular resistance even though the histologic classification of the pulmonary vascular disease was grade 1. The discrepancy in these two cases between the results of functional and histologic studies may be explained on the basis of hypoxia during the hemodynamic studies (Case 59) and of the associated mitral atresia with intact ventricular septum (Case 62).

TABLE III. Double Outlet Right Ventricle With Levocardia (Situs Solitus) and Pulmonary Stenosis

Case no.	Age(yr) & Sex	Location of VSD	Relation of Great Arteries	Oxygen Saturation (%)					Pressure (mm Hg)				Flow (liters/min per m²)		Resistance (units/m²)		Previous Surgical Shunt	Grade HPVD
				PA	SA	RV	MVB	LV	PA	SA	RV	LV	Q_p	Q_s	R_p	R_s		
PA>SA (6 cases)																		
1	14F	Subaortic	Side by side	91	84	72	67	. . .	33/10	117/79*	87/10	. . .	7.9	2.6	2.8	28.0	. . .	. . .
2	3M	Subpulmonary, infracristal	*d*-malposition	86	76	66	60	. . .	29/17	98/54	90/10	. . .	7.1	5.2	3.0	10.0	. . .	. . .
3	3M	Subpulmonary, infracristal	*d*-malposition	82	64	65	50	. . .	29/15	93/65	99/17	. . .	3.9	4.4	5.4	16.8	. . .	. . .
4	11M	Subpulmonary, infracristal	*d*-malposition	88	85	69	64	. . .	20/14	96/59	87/11	. . .	6.8	3.5	2.4	20.3	. . .	. . .
5	9F	Subpulmonary, infracristal	*l*-malposition	90	84	81	73	. . .	35/20	118/45	103/10	. . .	8.2	4.0	3.1	13.6	. . .	. . .
6	2F	Subpulmonary, infracristal	*l*-malposition	71	67	67	56	90	15/10	101/52	107/13	108/17	3.4	7.5	3.8	9.2	. . .	. . .
SA>PA (18 cases)																		
7	2F	Subaortic	Side by side	94	96	94	76	94	60/15	95/40	100/10	100/10	11.2	2.0	2.7	29.0	. . .	2–3
8	16M	Subaortic	Side by side	89	94	89	75	. . .	55/23	105/50*	75/15	91/13	5.5	4.7	4.1	17.0	. . .	. . .
9†	6F	Subaortic	Side by side	75	92	67	67	. . .	73/48	96/60	114/6	. . .	3.5	3.3	15.1	21.8	. . .	4
10	13M	Subaortic	Side by side	86	91	77	73	. . .	42/23	103/63	103/5	. . .	7.6	4.0	4.0	20.0	. . .	. . .
11	6/12F	Subaortic	Side by side	86	91	85	69	. . .	29/11	99/54	83/6	. . .	9.0	3.0	3.0	28.0	. . .	. . .
12	6M	Subaortic	Side by side	74	89	77	75	. . .	14/6	100/55*	83/5	. . .	3.3	5.7	3.0	12.2	. . .	. . .
13	2F	Subaortic	Side by side	79	85	67	68	. . .	40/9	90/47	86/6	. . .	5.5	5.1	3.7	9.3	. . .	. . .
14	1M	Subaortic	Side by side	66	84	65	63	. . .	19/13	81/53	72/12	. . .	3.3	5.2	5.8	10.0	. . .	. . .
15†	33F	Subaortic	Side by side	80	84	72	66	. . .	24/2	112/65	177/13	. . .	2.5	2.5	4.0	34.0	B-T	. . .
16	6M	Subaortic	Side by side	79	82	73	67	. . .	22/14	130/70	122/12	. . .	3.2	4.9	5.0	19.0	B-T	. . .
17	7M	Remote (AVC)	Side by side	75	77	69	61	87	18/14	120/62	127/12	115/10	2.1	3.1	7.6	26.1	B-T	1
18	6M	Remote (AVC)	Side by side	66	69	59	55	. . .	26/13	120/55*	107/10	. . .	1.8	6.1	10.6	16.7	B-T	2
19	5M	Subaortic	*d*-malposition	86	96	77	68	. . .	21/5	80/50	83/4	. . .	10.6	3.8	1.0	16.3	. . .	. . .
20	7M	Subaortic	*d*-malposition	72	92	55	52	92	43/20	101/65	92/13	102/14	3.5	1.5	7.8	54.6	. . .	. . .
21	14F	Subaortic	*d*-malposition	81	85	72	63	. . .	14/6	105/65	100/6	. . .	3.1	2.4	2.9	32.5	. . .	. . .
22	10F	Subaortic	*d*-malposition	68	79	65	69	. . .	19/8	103/67	97/12	. . .	1.8	3.8	6.6	21.0	(G)	. . .
23	13M	Subaortic	*d*-malposition	60	77	60	55	. . .	6/4	80/54	85/6	. . .	6.1	4.2	1.0	14.2	B-T	. . .
24	2F	Subaortic	*l*-malposition	64	74	60	55	. . .	32/18	89/48	91/7	93/15	3.1	4.8	7.4	12.9	. . .	. . .
PA=SA (5 cases)																		
25	20M	Subaortic	Side by side	81	81	63	65	. . .	14/2	75/38	90/5	. . .	2.6	2.7	2.3	18.6	B-T	. . .
26	12M	Subaortic	Side by side	80	80	80	62	74	17/9	128/77*	111/23	183/18	3.6	4.3	3.3	22.0	P	. . .
27	7F	Subaortic	Side by side	58	57	57	40	92	7/48	115/67	117/14	115/31	1.6	4.6	33.0	18.0	. . .	. . .
28	3F	Subaortic	*d*-malposition	90	90	90	61	97	68/25	100/51	85/5	89/2	9.4	3.9	4.1	17.0	. . .	. . .
29	9M	Subaortic	*d*-malposition	84	84	75	68	. . .	67/52	122/60	97/6	. . .	4.8	4.0	11.8	20.0	. . .	2

*Femoral arterial pressure not simultaneously recorded with right ventricular pressure, but pulmonary arterial and right ventricular pressures are taken from a withdrawal pressure recording.
†Subaortic stenosis significant on operative observation.
AVC = atrioventricular canal; B-T = Blalock-Taussig anastomosis; *d*-malposition = dextromalposition of great arteries; (G) = Glenn anastomosis (nonfunctioning shunt); HPVD = hypertensive pulmonary vascular disease as determined histologically; *l*-malposition = levomalposition of great arteries; LV = left ventricular; MVB = mixed venous blood; P = Potts anastomosis; PA = pulmonary arterial; Q_p = pulmonary flow; Q_s = systemic flow; R_p = pulmonary resistance; R_s = systemic resistance; RV = right ventricular; SA = systemic arterial; VSD = ventricular septal defect.

TABLE IV. Double Outlet Right Ventricle With Levocardia (Situs Solitus) Without Pulmonary Stenoisis

Case no.	Age (yr) & Sex	Location of VSD	Relation of Great Arteries	O_2 Saturation					Pressure				Flow		Resistance		Grade HPVD
				PA	SA	RV	MVB	LV	PA	SA	RV	LV	Q_p	Q_s	R_p	R_s	
A. With Pulmonary Vascular Obstructive Disease																	
PA>SA (12 cases)																	
30	2F	Subpulmonary, supracristal	Side by side	73	60	53	44	...	106/63	110/60	106/8	...	5.3	6.0	15.5	13.8	...
31	10F	Subpulmonary, supracristal	Side by side	89	79	...	64	...	108/73	115/70	109/10	...	6.6	3.4	11.5	25.0	...
32	14F	Subaortic	Side by side	91	83	90	61	...	127/66	130/80	118/7	...	5.8	2.3	14.8	42.2	...
33	9M	Subaortic	Side by side	89	83	89	67	88	120/67	108/76	120/8	120/7	10.2	5.4	7.4	17.6	3
34	6M	Subaortic	Side by side	88	81	73	65	...	84/45	100/55	88/11	...	6.7	3.1	9.1	21.9	...
35	8M	Subaortic	Side by side	86	84	62	62	...	99/58	106/64	98/14	...	6.5	3.4	11.0	22.9	3
36	3M	Subaortic	Side by side	86	71	66	51	...	90/60	90/60	88/4	...	6.7	4.4	10.4	15.9	...
37	4F	Subaortic	Side by side	88	75	76	53	97	80/40	80/50	80/6	80/7	7.8	3.8	6.4	16.0	3-4
38	10M	Subaortic	Side by side	76	68	69	52	...	98/65	107/74	89/11	...	2.8	3.8	27.0	22.0	...
39	6F	Subaortic, subpulmonary	Side by side	90	82	87	69	...	87/44	82/52	81/6	...	7.4	5.5	7.5	11.5	4
40	2M	Subaortic, subpulmonary	Side by side	87	72	71	59	...	99/44	98/53	90/1	...	8.4	4.5	7.4	15.0	2-3
41	11F	Subpulmonary, infracristal	Levomalposition	77	54	49	42	...	101/74	130/71	110/12	...	3.9	4.6	22.1	19.6	...
SA>PA (6 cases)																	
42	10M	Subaortic	Side by side	80	94	83	55	...	72/27	81/51	78/7	...	3.7	1.8	11.4	33.8	...
43	9M	Subaortic	Side by side	75	90	72	65	...	122/60	120/65	112/4	...	5.2	4.5	15.0	19.0	...
44	5M	Subaortic	Side by side	72	78	68	57	...	95/51	95/50	91/4	...	4.0	4.4	16.5	14.7	...
45	16F	Subaortic	Side by side	52	72	46	42	...	124/79	132/84	123/5	...	1.1	2.4	85.0	41.7	...
46	7F	Suboartic	Side by side	81	90	81	73	...	82/43	82/50	86/7	90/12	6.5	4.7	9.5	13.0	...
47	2F	Remote (AVC)	Side by side	88	90	92	72	...	89/42	87/35	87/9	...	14.0	5.2	4.6	10.6	4
PA=SA (3 cases)																	
48	5F	None (intact septum)	Levomalposition	80	79	79	62	...	87/57	110/65	92/4	...	4.8	5.1	14.0	15.4	...
49	5M	Remote (AVC)	Side by side	86	86	85	68	87	94/45	90/58	89/2	85/7	6.9	2.7	9.2	23.3	...
50	16F	Subaortic	Side by side	67	67	80	50	...	104/70	132/67	123/18	...	5.0	5.2	16.2	17.1	...
B. Without Pulmonary Vascular Obstructive Disease																	
PA>SA (7 cases)																	
51	2/12F	Subpulmonary, supracristal	Side by side	89	86	77	60	...	64/22	69/36	64/6	...	7.1	2.3	5.0	20.4	...
52	1/12F	Subpulmonary, supracristal	Side by side	87	80	75	52	...	62/26	70/48	63/3	...	9.7	3.2	4.0	18.8	...
53	5F	Subpulmonary, infracristal	*d*-malposition	89	85	84	68	...	85/50	99/62	88/7	...	8.6	4.0	7.0	18.0	...
54	4/12M	Subpulmonary, infracristal	*d*-malposition	93	88	84	64	...	83/55	80/57	85/19	...	14.0	1.9	4.5	37.7	...
55	11M	Subpulmonary, infracristal	*d*-malposition	92	82	87	69	...	94/56	110/64	94/10	...	13.8	5.2	5.0	15.2	...
56	13F	Subaortic	Side by side	91	85	83	72	...	98/52	96/62	102/14	...	14.4	6.7	4.6	10.9	...
57	4M	Remote (straddling mitral valve)	Side by side	69	65	75	63	...	23/13*	100/62	124/13	...	4.2	3.4	3.8	22.0	...
SA>PA (3 cases)																	
58	7F	Subaortic	*d*-malposition	88	97	88	74	...	70/30	88/60	75/5	...	8.8	3.5	4.9	19.7	...
59	2/12F	Subaortic	Normal	59	71	58	52	...	79/47	70/52	73/7	...	3.4	6.6	17.1	8.9	1
60	1M	Subaortic	Normal	89	94	89	62	...	73/45	105/80	79/8	...	11.5	2.5	4.7	36.0	...
PA=SA (2 cases)																	
61	18M	Subaortic	*d*-malposition	92	92	90	77	...	88/47	107/68	85/6	...	12.2	3.0	5.0	26.9	...
62	2/12F	None (intact septum mitral valve atresia)	*d*-malposition	80	81	80	63	...	83/33	95/50	88/3	...	4.2	3.5	11.0	19.0	1

*Pulmonary arterial banding. Abbreviations and units as in Table III.

TABLE V

Differences in Oxygen Saturation in 62 Cases of Double Outlet Right Ventricle

Oxygen Saturation	Cases (no.)	Range of Oxygen Saturation (%)		Difference (%)	
		PA	SA	Range	Mean
PA>SA	25	71–93	54–88	3–23	8.2
SA>PA	27	52–94	69–97	2–20	8.8
PA=SA	10	57–92	57–92	<2	<2

PA = pulmonary arterial; SA = systemic arterial.

TABLE VI

Relation of Ventricular Septal Defect, Oxygen Saturation, Pulmonary Stenosis and Pulmonary Vascular Obstructive Disease in 62 Cases of Double Outlet Right Ventricle

Location of VSD	Cases (no.)	Oxygen Saturation	With PS	Without PS		Total
				PVOD	No PVOD	
Subpulmonary	13	PA>SA	5	3	5	13
Subaortic	40	PA>SA	1	7	1	9
		SA>PA	16	5	3	24
		PA=SA	5	1	1	7
Subaortic and subpulmonary	2	PA>SA	0	2	0	2
Remote (atrioventricular canal)	5	PA>SA	0	0	1	1
		SA>PA	2	1	0	3
		PA=SA	0	1	0	1
No VSD (intact septum)	2	PA=SA	0	1	1	2
Total	62		29	21	12	62

PA = pulmonary arterial; PS = pulmonary stenosis; PVOD = pulmonary vascular obstructive disease; SA = systemic arterial; VSD = ventricular septal defect.

Associated Conditions

The 62 patients in this study had associated anomalies in addition to the basic conditions (Table II). Pulmonary stenosis was observed in just less than half of the cases (29 of the 62 patients). The pulmonary stenosis was usually produced by a combination of valvular and subpulmonary infundibular stenosis.

Atrial septal defect at the fossa ovalis, the defects being of varying sizes, was observed in 16 of the 62 patients. In two patients, an atrial septal defect was associated with an intact ventricular septum; one patient (Case 48) had parachute mitral valve and the other (Case 62) had mitral atresia. In these patients, the atrial septal defect was the only outlet of the left side of the heart.

Three patients (Cases 18, 47 and 49) had an atrial septal defect in the lowermost part of the atrial septum as part of persistent common atrioventricular canal, with the common anterior leaflet undivided and unattached to the ventricular septum (Rastelli type C).[17] In each of these patients, the ventricular septal defect was remote from each semilunar valve. Of the other two patients with remote ventricular septal defect, one (Case 17) had a ventricular septal defect of the atrioventricular canal type, whereas the other (Case 57) had a straddling mitral valve. Three patients (Cases 7, 28 and 47) had a small muscular ventricular septal defect in addition to the classic defect of double outlet right ventricle.

Patent ductus arteriosus was seen in 10 patients, only 1 of whom (aged 2 years) had associated pulmonary stenosis. The two youngest patients were 1 month and 4 months of age, respectively; the ages of the other eight patients ranged from 1 to 13 years.

Mitral valve abnormalities were observed in four patients: straddling mitral valve in one (Case 57), parachute mitral valve in two (Cases 26 and 48) and mitral valve atresia in one (Case 62). The last patient was one of the two patients with an intact ventricular septum.

Subaortic stenosis was noted hemodynamically in two patients (Cases 9 and 15). This process appeared to have resulted from hypertrophy of the parietal limb of the crista supraventricularis.

Coarctation of the aorta was observed in only one patient (Case 52), a one month old infant with Taussig-Bing anomaly.

Origin of the anterior descending coronary artery from the right coronary artery was seen in five patients (Cases 11, 12, 16, 24 and 28), all of whom had pulmonary stenosis. From its anomalous origin, this vessel crossed the outflow part of the right ventricle to reach the anterior interventricular sulcus. Three of the patients had the great arteries in a side by side relation, and two had malposition.

Hemodynamic Observations

The hemodynamic data and pertinent anatomic findings in the 62 cases are summarized in Tables III and IV, the patients being classified into those (1) with pulmonary stenosis, (2) without stenosis but with pulmonary vascular obstructive disease, and (3) without either pulmonary stenosis or pulmonary vascular obstructive disease.

The patients were classified into three groups according to arterial saturation patterns (Table V). (1) pulmonary arterial saturation greater than systemic arterial saturation by as much as 23 percent, with a mean difference of 8.2 percent (25 patients); (2) systemic arterial saturation greater than pulmonary arterial saturation by as much as 20 percent, with a mean difference of 8.8 percent (27 patients); and (3) pulmonary arterial saturation equal to systemic arterial saturation (less than 2 percent difference) (10 patients).

These hemodynamic patterns were not related to such factors as (1) the relation of the great arteries; (2) presence or absence of pulmonary stenosis; (3) presence or absence of pulmonary vascular obstructive disease or (4) functioning systemic-pulmonary arterial shunts. However, there was a tendency for a relation between relative saturation values and the position of the ventricular septal defect (Table VI).

Position of ventricular septal defect and oxygen saturation values: In each of the 13 patients with subpulmonary ventricular septal defect, the pulmonary

arterial oxygen saturation was greater than systemic arterial saturation, regardless of the presence or absence of pulmonary stenosis or pulmonary vascular obstructive disease. None of the 13 patients had had a surgical systemic pulmonary arterial shunt (Table VI). When the ventricular septal defect was subaortic, the saturation pattern varied. In 24 of the 40 patients with a subaortic ventricular septal defect, the systemic arterial saturation was greater than the pulmonary arterial saturation. In 7 of the 10 patients with subaortic ventricular septal defect and malposition of the great vessels, the systemic arterial saturation was greater than the pulmonary saturation. Six of the seven (Cases 19 to 24) had pulmonary stenosis, and the seventh (Case 58) had neither pulmonary stenosis nor pulmonary vascular obstructive disease. The remaining three patients with subaortic ventricular septal defect and malposition of the great vessels (Cases 28, 29 and 61) had equal pulmonary and systemic arterial oxygen saturation levels, and two of the three (Cases 28 and 29) had pulmonary stenosis.

Ventricular septal defect and side by side great arteries: Of the 28 patients with the combination of subaortic ventricular septal defect and side by side relation of the great arteries, 15 had systemic arterial saturation greater than pulmonary saturation. Each of these had either pulmonary stenosis (10 patients) or pulmonary vascular obstructive disease (5 patients). Nine of the 28 patients had pulmonary saturation greater than systemic; 6 of these had pulmonary vascular obstructive disease and 2 had increased pulmonary flow without pulmonary stenosis but with mild elevation of pulmonary resistance. The remaining four patients had equal pulmonary and systemic arterial oxygen saturation levels; three of these had pulmonary stenosis, and one had pulmonary vascular obstructive disease.

Two patients who had subaortic and subpulmonary ventricular septal defect had pulmonary arterial saturation greater than systemic arterial saturation.

The five patients with the ventricular septal defect remote from both semilunar valves had dissimilar arterial saturation levels. One patient had pulmonary arterial oxygen saturation greater than systemic, three had greater systemic saturation and one had equal saturation.

In the two patients with intact ventricular septum the levels of oxygen saturation were equal in the pulmonary and systemic arteries.

Comment

Most reports on double outlet right ventricle indicate that the great arteries most commonly lie side by side with the aorta to the right of the pulmonary trunk. Our study broadens this view. Although, in our series, most patients (39 patients, 63 percent) had this arrangement, 19 (30 percent) with malposition of the great arteries had the aorta anterior to the pulmonary trunk. An unusual situation occurred in two patients in that the great arteries were normally related.

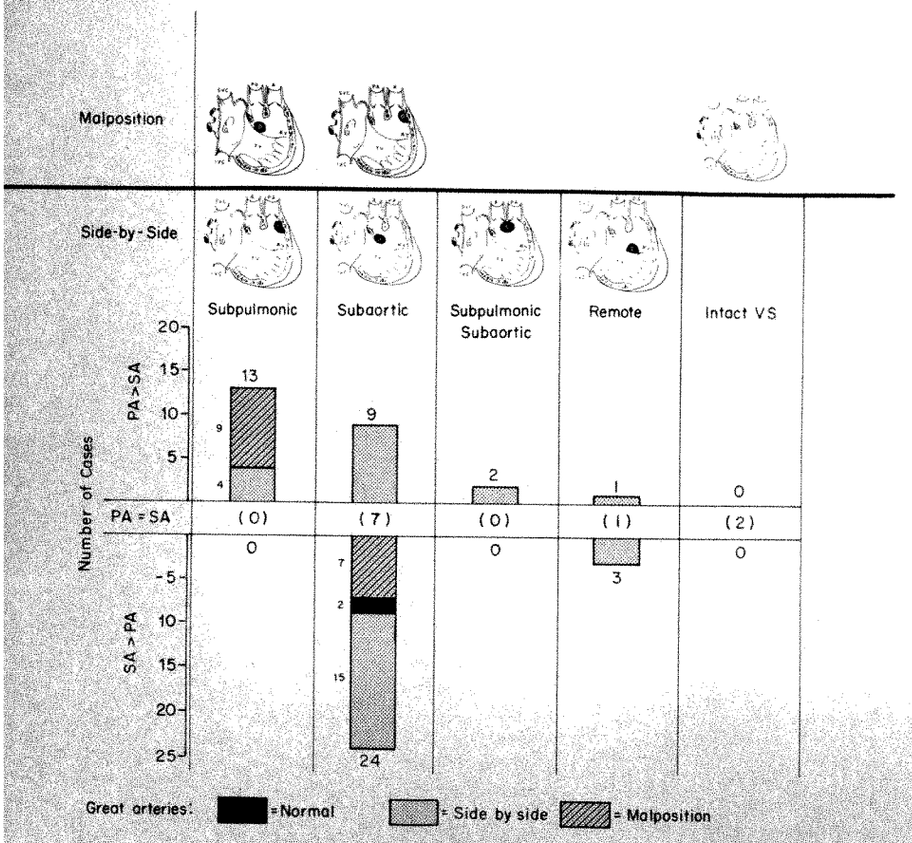

FIGURE 2. Diagrammatic representation of anatomic variants of double outlet right ventricle. Distribution of variants according to oxygen saturation and location of ventricular septal defect. PA = pulmonary arterial oxygen saturation; SA = systemic arterial oxygen saturation; VS = ventricular septum.

The most common combination of arrangement of great arteries and position of a ventricular septal defect was a side by side arterial relation and a subaortic ventricular septal defect.

Surgical Considerations

Preoperatively, it is important not only to identify the condition of double outlet right ventricle but also to determine the position of the ventricular septal defect relative to the semilunar valve because the conditions require different surgical procedures, depending on the anatomic features. In double outlet right ventricle and subaortic ventricular septal defect with the great arteries in a side by side relation (Fig. 1, top left) or in malposition (Fig. 1, bottom right), the repair is accomplished by creating an intraventricular baffle that conducts left ventricular blood to the aorta.[8,18–21] In double outlet right ventricle and subpulmonary ventricular septal defect with great arteries in a side by side relation (Fig. 1, top right) in malposition (Fig. 1, bottom left), the repair is accomplished either by creating an intraventricular conduit that conducts left ventricular blood to the pulmonary arteries and performing the Mustard procedure[22,23] or by creating an intraventricular baffle directing the left ventricular blood to the aorta and connecting the right ventricle to the pulmonary artery by use of a conduit (the Rastelli operation).[24,25] The double outlet right ventricle with great arteries in a side by side relation and remote (atrioventricular canal) position of the ventricular septal defect has not been successfully repaired as yet.[26] In double outlet right ventricle with great arteries in a side by side relation with subaortic and subpulmonary ventricular septal defect, the repair is also accomplished by creating an intraventricular baffle that conducts left ventricular blood to the aorta.

Diagnostic Considerations

Large film biplane angiocardiography is the most important diagnostic aid presently available. However, knowledge of the levels of oxygen saturation of blood in the pulmonary artery as compared with a systemic artery can be helpful. The data in our series indicate that when, in double outlet right ventricle, the systemic arterial saturation is higher than the pulmonary saturation, the presence of a subaortic ventricular septal defect is a strong likelihood (Fig. 2). However, while subpulmonary ventricular septal defect exhibits a greater pulmonary than systemic saturation, the same features may be observed in subaortic ventricular septal defect with side by side relation between the great arteries.

It is of interest that none of our patients with subaortic ventricular septal defect and either dextromalposition or levomalposition had pulmonary saturation greater than systemic saturation. Perhaps this is explained by the fact that the subaortic ventricular septal defect is related more closely to the malpositioned aortic valve than to the valve of a "side by side" aorta. Although saturation levels were equal in the aorta and pulmonary trunk in each of the two patients with intact ventricular septum, eight other patients with this hemodynamic feature had ventricular septal defect in various positions.

Associated Anomalies

Double outlet right ventricle is associated with other anomalies. In addition to pulmonary stenosis, atrial septal defect at the fossa ovalis occurred in about 25 percent. Patent ductus arteriosus occurred in 10 patients, and only 1 of the 10 had pulmonary stenosis. Important also is the occurrence of persistent common atrioventricular canal (Rastelli type C), as is true for anomalies of the mitral valve.

Important surgically is the tendency for patients with pulmonary stenosis to have the anterior descending coronary artery originate from the right coronary artery. This presents the surgical problem of a large coronary artery crossing the general area in which right ventriculotomy is generally performed.

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Metabolic Consequences of Glucose-Insulin-Potassium Infusion in Treatment of Acute Myocardial Infarction

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Eighteen patients treated with glucose-insulin-potassium infusion for anaerobic support of acutely ischemic myocardial tissue were studied to ascertain the metabolic consequences of this therapy for acute myocardial infarction. Twelve patients with acute myocardial infarction were treated in a conventional manner and served as control subjects. The glucose-insulin-potassium solution was composed of 300 g of glucose, 50 units of regular insulin and 80 mEq of potassium ion per liter, and was infused at a rate of 1.5 ml/kg per hour through the right atrial port of an indwelling Swan-Ganz thermodilution catheter. Serial measurements of serum electrolytes, cardiac and hepatic enzymes, glucose and osmolality were obtained every 4 to 6 hours for 4 days. Twenty-four hour urinary volume and potassium levels were measured daily. Pulmonary arterial end-diastolic pressure was measured hourly and the cardiac index daily for the duration of the study. Serum potassium increased to 5 mEq/liter during the infusion and to more than 6 mEq/liter after infusion in 28 percent of patients. No recognizable complications or arrhythmias accompanied this transient hyperkalemia. Potassium balance studies revealed a net total body potassium ion gain of 120 mEq during the study. The second most frequent finding was an elevation of serum glucose (mean 175 mg/100 ml); in all instances this was controlled with supplemental administration of insulin. The serum osmolality and fluid balance remained normal in all patients during the study. Serum glutamic oxaloacetic transaminase (SGOT) and fraction 5 of lactic dehydrogenase (LDH) were increased in 34 percent of the patients during the last 12 to 18 hours of the glucose-insulin-potassium infusion. Characterization of these enzymes suggested a hepatic origin for these changes. This study suggests that glucose-insulin-potassium infusion is a relatively safe procedure in which postinfusion hyperkalemia is the most serious potential complication.

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Glucose-insulin-potassium solutions have been used in various concentrations and infusion rates[1–3] for support of ischemic tissue during acute myocardial infarction. Recent evidence[4] has indicated that this therapy is most effective when a concentration of 300 g of glucose, 80 mEq of potassium ion and 50 units of regular insulin per liter is given at a rate of 1.5 or more ml/kg per hour. This concentration and infusion rate result in a daily volume load of 3 to 4 liters and a daily potassium load of 160 to 240 mEq. Although no mortality related to the clinical use of glucose-insulin-potassium has been reported, morbidity and mortality theoretically could occur as a result of possible volume overload and significant increase or decrease in serum glucose or potassium.

The purpose of this study was to evaluate the potential metabolic consequences of glucose-insulin-potassium therapy in 18 patients during the early phase of acute myocardial infarction.

Methods

All patients in this study were admitted directly to the Myocardial Infarction Research Unit of the University of Alabama Medical Center where the diagnosis of acute myocardial infarction was made on the basis of a typical history, pathologic Q wave development or evidence of subendocardial injury in the electrocardiogram and a serum enzyme increase characteristic of infarction.

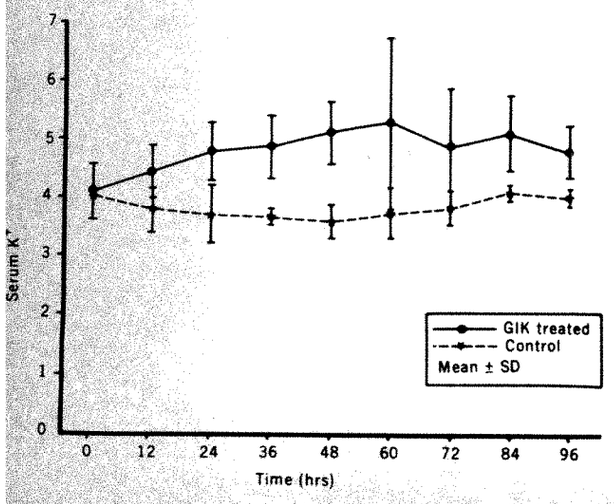
Eighteen consecutive patients with acute infarction were treated with a glucose-insulin-potassium infusion for 48 hours beginning within 12 hours of the onset of symptoms of the infarction. Twelve consecutive patients with myocardial infarction were treated in a more conventional manner and received a solution of either 0.45 percent sodium chloride or 5 percent dextrose in water as an infusate in amounts similar to the glucose-insulin-potassium infusion or at a rate of 10 ml/hour. An additional seven patients without evidence of acute myocardial infarction or hepatic dysfunction were given a glucose-insulin-potassium infusion to assess the influence of this solution on hepatic and myocardial enzyme activity levels. The patients were allowed an unlimited clear liquid diet, and a rigorous record was maintained of all oral and intravenous fluid intake.

Six patients in the treated infarction group and four in the control infarction group had a history of a prior myocardial infarction. One patient in the treated group had cardiogenic shock on admission and two patients had clinical and radiologic evidence of pulmonary edema. No patient in the control group had evidence of cardiogenic shock, but two in this group had pulmonary edema. The remaining patients in both groups had no evidence of left ventricular dysfunction or had only a third sound gallop.

Procedures: After informed consent was obtained, right heart catheterization was performed utilizing a triple lumen Swan-Ganz thermistor catheter positioned in the main pulmonary artery. Initial measurements of pulmonary arterial end-diastolic pressure, cardiac index, right atrial pressure, serum electrolytes, urea nitrogen, creatinine, glucose and osmolality and cardiac enzymes including lactic dehydrogenase (LDH) isoenzyme fractionation were obtained to establish control levels. The first of four 24 hour collections of urine for volume and potassium determinations was subsequently begun. Cardiac rhythm was continuously monitored at a central station.

The glucose-insulin-potassium solution was infused continuously for 48 hours through the right atrial outlet of the Swan-Ganz line at a rate of 1.5 ml/kg per hour. The pulmonary arterial outlet of the Swan-Ganz line was kept patent with an infusion of a solution of 0.45 percent sodium chloride containing 5 units/ml of heparin at a rate of 10 ml/hour.

Serial measurements of blood chemistry values were made every 6 hours. Pulmonary arterial end-diastolic pressure (as a reflection of left ventricular filling pressure[5]) was measured every 1 to 2 hours and cardiac index every 24 hours. Aliquots of urine were checked every 4 hours for glucose and ketones. Serum chemistry values were measured on Technicon autoanalyzers; lactic dehydrogenase isoenzymes were separated and measured by paper electrophoresis. Serum osmolality was determined by the freezing point depression method. Student's t test was used to assess differences of the means. Results are reported as mean values ± standard deviation.



IGURE 1. Comparison of mean serum potassium ion values (mEq/liter) 1 17 patients receiving glucose-insulin-potassium (GIK) infusion and 1 12 patients receiving a solution of 0.45 percent sodium chloride or percent dextrose in water. The glucose-insulin-potassium solution vas infused between 0 and 48 hours. Values shown are mean values ± standard deviation (SD).

Results

Clinical course: Two patients in the group treated with glucose-insulin-potassium died, one from recurrent ventricular fibrillation 36 hours after treatment was begun and the other from a second myocardial infarction 4 hours after the infusion was discontinued. One patient in the control group died on the 2nd day of treatment from cerebral ischemia sustained while he was being resuscitated before hospital admission.

Hemodynamics: The mean pulmonary arterial end-diastolic pressure and cardiac index were not significantly different in the patients treated with glucose-insulin-potassium and control patients. Hemodynamic values in both groups remained stable throughout the study.

Serum potassium: Figure 1 compares the serum potassium ion response in 17 patients who received glucose-insulin-potassium for 48 hours with that of 12 patients who received a solution of 0.45 percent sodium chloride or 5 percent dextrose in water. Serum potassium ion in treated patients gradually increased to a mean of 5 mEq/liter at the end of 48 hours, a level 1.5 mEq/liter higher than that of control patients. Six hours after discontinuation of glucose-insulin-potassium infusion the mean serum potassium ion level rose to 5.5 mEq/liter and 12 hours after discontinuation it was 5.3 mEq/liter. Serum potassium ion increased markedly (more than 6 mEq/liter) in 28 percent of patients but the increase was not pronounced in the remaining 72 percent. One patient whose data were not included in Figure 1 had a serum potassium ion value of 7.3 mEq/liter after 24 hours of glucose-insulin-potassium infusion. The infusion was discontinued and the patients promptly treated for hyperkalemia. Patients experiencing marked elevations in serum potassium ion levels after infusion were treated vigorously with sodium polystyrene sulfonate, orally and by rectal enema, and when appropriate with an intravenous bolus injection of glucose and insulin for temporary corrective effect.

Renal function: Before infusion of glucose-insulin-potassium, the patients' renal function was ascertained by assessment of serum creatinine and urea nitrogen

levels. The patients in this study had a mean creatinine clearance rate of 95 ± 21 ml/min (range 65 to 130) and a mean serum creatinine value of 1.1 ± 0.4 mg/100 ml. Azotemia on a prerenal basis was not a contraindication for glucose-insulin-potassium therapy. Patients experiencing cardiogenic shock were given glucose-insulin-potassium provided the baseline urinary flow was at least 15 to 20 ml/hour and also responsive to diuretic therapy.

Potassium balance: Figure 2 depicts the total potassium balance for the 4 days of the study. There was a net gain in potassium ion of 170 mEq after 48 hours of glucose-insulin-potassium infusion. After the occurrence of potassium ion elevation there was a net loss of 50 mEq of potassium ion during the 3rd and 4th days of the study, most of the loss occurring during the 3rd day. Thus, a net gain in total body potassium ion of 120 mEq is apparent from Figure 2, although a portion of this potassium ion may have been lost through the gastrointestinal tract and would therefore not be accounted for in this study.

Serum glucose: Figure 3 compares the mean serum glucose concentration for all 18 patients given glucose-insulin-potassium solution with values in 12 control patients. Although the serum glucose level in treated patients was persistently higher than in control subjects, this difference was not statistically significant. Attempts were made to maintain the serum glucose level below 250 mg/100 ml and, as indicated in Figure 3, this effort was generally successful during the last 36 hours of the infusion. Urinary glucose, as estimated by a Urostik®, was generally absent or present only in trace amounts.

Osmolality: Figure 4 compares the serum osmolality of the 18 patients treated with glucose-insulin-potassium with that of the 12 control patients. There was no statistically significant difference between these curves. However, the serum osmolality of the treated patients declined by 8 milliosmols/liter during the 48 hours of glucose-insulin-potassium infusion.

Fluid balance: The bar graphs in Figure 5 depict the total fluid intake and output of the patients treated with

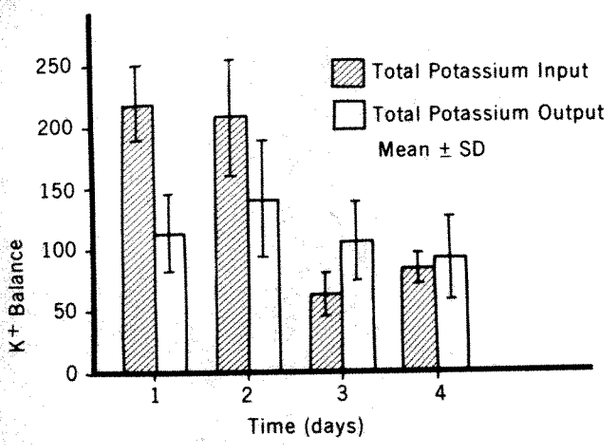


FIGURE 2. Potassium ion balance (mEq/24 hours) in the patients receiving glucose-insulin-potassium infusion. Input exceeded output only during the first 2 days of the study.

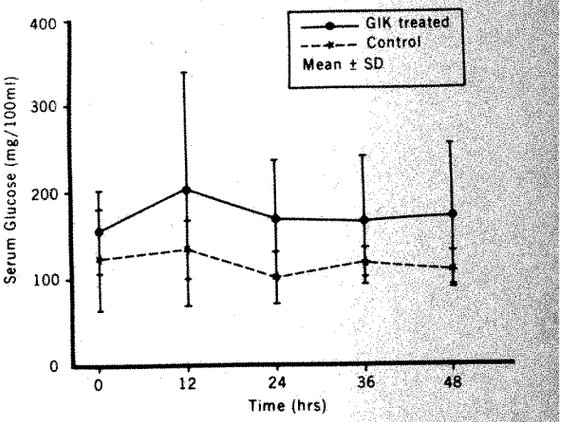


FIGURE 3. Comparison of mean serum glucose values in patients treated with glucose-insulin-potassium (GIK) and in seven untreated control patients. Although serum glucose values during infusion were persistently higher in treated than in untreated patients, there was no statistical difference between the two curves.

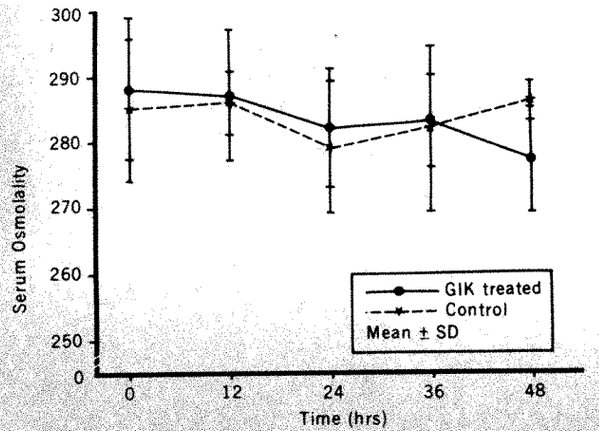


FIGURE 4. Comparison of mean serum osmolality (milliosmols/liter) in patients treated with glucose-insulin-potassium (GIK) and in control patients.

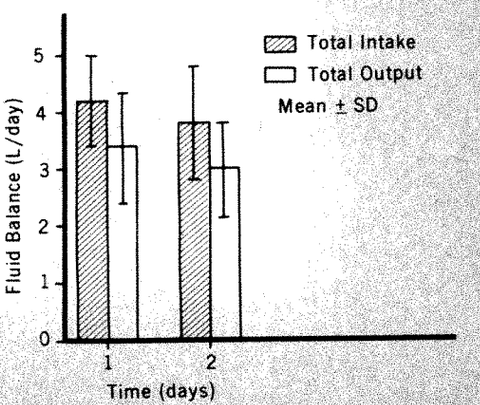


FIGURE 5. Total daily fluid intake and output during the 48 hours o glucose-insulin-potassium (GIK) infusion in treated patients. There wa no statistical difference between fluid intake and output.

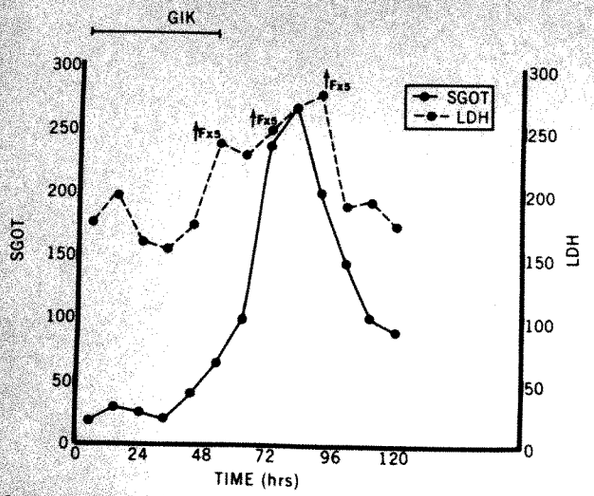


FIGURE 6. Total serum SGOT and LDH activity (IU/liter) in a patient without myocardial infarction treated with glucose-insulin-potassium (GIK). Both enzymes, especially LDH_5 (F_{x5}), increased during the terminal phase of the infusion.

glucose-insulin-potassium. During day 1 of the infusion there was a mean intake of 4.1 liters and a mean output of 3.3 liters; on day 2 the mean intake was 3.7 liters and the mean output 2.9 liters, leaving a positive balance of 800 ml for each day. It is probable that insensible water loss of 500 to 700 ml/day accounts for most of the reduction in output and thus for most of the positive fluid balance in these patients.

Hepatic enzyme alteration: In 6 (35 percent) of 17 patients treated with glucose-insulin-potassium, lactic dehydrogenase isoenzyme fraction 5 (LDH_5) increased during the last 12 to 18 hours of infusion. Concomitant with this increase was an increase in serum glutamic oxaloacetic transaminase (SGOT) activity to 150 to 400 IU/liter. In three of seven patients without evidence of an acute myocardial infarction who were treated with glucose-insulin-potassium, a similar enzyme response was observed late in the course of infusion (Fig. 6). However, this enzyme elevation was limited to LDH_5, SGOT and (in one patient) serum glutamic pyruvate transaminase (SGPT). No change from control levels of serum alkaline phosphatase, bilirubin, protein electrophoretic pattern or clotting studies occurred in any patient studied.

Discussion

Glucose-insulin-potassium infusion has been under study for several years[6] for treatment of angina pectoris and acute myocardial infarction. Since 1969, Sodi-Pallares and his group[7] have advocated continuous infusions of high concentrations of glucose, insulin and potassium for treatment of myocardial infarction. A previous study from our group[8] showed that infusion of glucose-insulin-potassium directly into the pulmonary artery may result in localized pulmonary infiltrates and ventilation-perfusion abnormalities, but no severe complications of glucose-insulin-potassium infusion into the right atrium have been reported to date. This study confirms in detail that the infusion can be controlled so that it is a relatively safe procedure provided a few simple guidelines are followed.

Electrolytes: The most frequent metabolic aberration of glucose-insulin-potassium therapy encountered in this study was hyperkalemia, which occurred in 28 percent of patients. It was most prevalent after discontinuation of the infusion, and in one patient it was associated with T wave changes in the electrocardiogram. The patients who had hyperkalemia had a normal creatinine clearance rate and a serum potassium ion level of less than 5.5 mEq/liter throughout the infusion. One patient with hyperkalemia had a history of analgesic abuse and conceivably may have had interstitial nephritis as an underlying renal problem. As previously noted, glucose-insulin-potassium infusion was discontinued after 24 hours in one patient because of hyperkalemia. Severe hyperkalemia (potassium ion greater than 6 mEq/liter) was treated with sodium polystyrene sulfonate (Kayexalate®) orally or by rectal enema or by reducing the potassium ion in the infusate as originally proposed by Sodi-Pallares et al.[7]

A decrease in serum sodium ion of 6 to 10 mEq/liter occurred routinely during glucose-insulin-potassium infusion, but values returned to normal 12 to 24 hours after completion of the infusion. Serum sodium ion level did not drop below 130 mEq/liter during this study.

Potassium balance during the 48 hours of glucose-insulin-potassium infusion was routinely positive (Fig. 2). However, renal compensation to the potassium ion load began to occur on the second day, so that a net loss of potassium ion was apparent by the 3rd day. Nevertheless, the patients had a gain of approximately 120 mEq of potassium ion and at the completion of the study they had normal serum potassium ion levels.

Blood urea nitrogen: Blood urea nitrogen decreased in all patients treated with glucose-insulin-potassium, values ranging from 4 to 10 mg/100 ml by the end of the infusion, compared with preinfusion values of 15 to 25 mg/100 ml. This decrease presumably reflects the anabolic condition of the patients during infusion or a decrease in hepatic synthesis of urea during infusion, or both.

Glucose: Hyperglycemia and an abnormal glucose tolerance curve are frequently observed after acute myocardial infarction.[9–11] This finding probably reflects suppression of insulin release from the pancreas due to increased sympathetic activity coupled with poor pancreatic perfusion.[12,13] The majority of patients in our study were hyperglycemic before infusion of glucose-insulin-potassium was begun, but the serum glucose level remained remarkably stable for the duration of the study after slight variations in the insulin dose were made during the first 12 hours of the infusion. Additional insulin was given subcutaneously when serum glucose values were greater than 250/100 ml, and insulin was decreased in the infusate by 5 to 10 units/liter when hypoglycemia occurred (only one patient in this study).

Osmolality: The gradual reduction in the serum osmolality during the glucose-insulin-potassium infusion

was probably secondary to the decrease in serum sodium and urea nitrogen, which was observed in all patients. In each case, after the glucose-insulin-potassium was discontinued the serum osmolality returned to the preinfusion level as serum sodium and urea nitrogen levels rose to the normal range.

Fluid balance: Fluid intake and output were uniformly well balanced in all patients receiving glucose-insulin-potassium, with no evidence of hyper- or hypovolemia in any patients during the infusion study. Patients who underwent hemodynamic monitoring had no left ventricular overload as assessed by pulmonary arterial end-diastolic pressure determination.[5]

Enzyme alterations: The enzyme alterations that occurred in 42 percent of control patients without myocardial infarction who were treated with glucose-insulin-potassium suggest a hepatic origin for these changes. This is difficult to reconcile with the finding that LDH_5 increased in two patients who were not given glucose-insulin-potassium but who were otherwise treated in the same manner as the patients given glucose-insulin-potassium. However, SGOT did not increase in these two patients. The significance of the enzyme changes during glucose-insulin-potassium infusion is not clear, but caution must be exerted over falsely diagnosing acute myocardial infarction on the sole basis of enzyme elevation. A liver biopsy or an enzyme of specific hepatic origin such as ornithine carbamyltransferase[14,15] would be of diagnostic importance in elucidating the effects of glucose-insulin-potassium on hepatic function.

Clinical implications: This study has demonstrated that, although glucose-insulin-potassium infusion is a safe procedure, serum electrolytes and glucose levels should be serially monitored. Hyperkalemia during glucose-insulin-potassium infusion should be treated by reducing the concentration of potassium ion in the infusate, whereas hyperkalemia after discontinuation of the infusion should be treated with sodium polystyrene sulfonate orally or by rectal enema. Hyperglycemia may best be managed with additional insulin. In addition, an increase in total serum SGOT and LDH activity occurring late in the infusion period should not prompt one to diagnose a myocardial infarction until serum creatine phosphokinase and LDH isoenzymes are evaluated.

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Diabetic Treatment and Primary Ventricular Fibrillation in Acute Myocardial Infarction

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The relation between mode of therapy and mortality rate and incidence of primary ventricular fibrillation was studied in 265 patients with diabetes mellitus and acute myocardial infarction. Sixty patients were being treated with diet only, 54 were receiving insulin and 151 were taking oral hypoglycemic agents. Fourteen patients (5.3 percent) had primary ventricular fibrillation, and all but one died. No statistically significant association was found between the incidence of primary ventricular fibrillation and the type of treatment for diabetes mellitus. Sixty-four (24.2 percent) of the 265 patients died during hospitalization. Mortality was greater among diabetic patients receiving oral therapy. However, after adjusting for age and sex, the difference among these three treatment regimens did not reach the $P < 0.05$ level of significance.

The controlled trial of the University Group Diabetes Program (UGDP) investigators revealed an increased rate of death from cardiovascular disease among diabetic patients taking tolbutamide[1,2] and phenformin.[3] Although criticism concerning the study was raised,[4] a recent review by the Biometric Society[5] concluded that the shortcomings of the UGDP study were not sufficient to invalidate the results.

Soler et al.[6] reported an increased frequency of primary ventricular fibrillation after acute myocardial infarction among diabetic patients receiving oral hypoglycemic agents. They noted several episodes of this arrhythmia after the patients were transferred from the coronary care unit and suggested that a longer period of intensive care may be necessary for diabetic patients receiving oral therapy.

This study investigated the association between primary ventricular fibrillation and survival in diabetic patients admitted to coronary care units and the treatment of their diabetes.

Method

The hospital records were reviewed of all patients admitted to the coronary care units of the three participating hospitals from January 1971 through June 1974 with a diagnosis of acute myocardial infarction and known diabetes mellitus. The three participating hospitals included two voluntary and one municipal hospital. All patients had constant oscilloscopic monitoring during their stay in the coronary care unit. They were transferred to the medical service of the respective hospital after discharge from the coronary care unit. The diagnosis of acute myocardial infarction was substantiated by typical electrocardiographic and serial enzyme changes. The classification of diabetic treatment was made depending on the type of medication taken immediately before hospital admission. Patients taking both orally administered drugs and insulin were categorized as receiving oral therapy only.

A diagnosis of ventricular fibrillation was established when the typical pattern was seen on an oscilloscope or recorded electrocardiographically and was accompanied by sudden complete cardiovascular collapse. Only instances of primary ventricular fibrillation were recorded. Patients who had episodes of ventricular fibrillation during periods of marked or terminal congestive heart failure, cardiogenic shock or complete heart block were not included in the group with

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fibrillation. The decision to exclude them from this group was made without knowledge of the therapy they were receiving.

Two clinical epidemiologists reviewed all records. To control for bias, the study was designed with two separate work sheets; one for cardiac diagnosis and the other for diabetes mellitus. Each medical record was first read by one technician who recorded the cardiac data and then later by the second technician for a diabetic history. There was no communication about individual records between them. Doubtful records were checked by one of the investigators.

Results

Two hundred sixty-five patients with known diabetes were admitted with a diagnosis of acute myocardial infarction. There were 60 patients treated with diet only, 54 receiving insulin therapy and 151 treated with oral hypoglycemic agents (Table I).

Ventricular fibrillation: Fourteen patients (5.3 percent) had primary ventricular fibrillation, and all but one died. The time of onset of this arrhythmia and the diabetic treatment on admission are shown in Table II. The incidence of primary ventricular fibrillation for each group is shown in Table III. These data did not reveal any statistically significant association between the incidence of primary ventricular fibrillation and the type of management of diabetes mellitus ($P > 0.50$).

Mortality: Sixty-four (24.2 percent) of the 265 patients died during hospitalization. Analysis of the mortality rate according to type of diabetic treatment (Table IV) shows a higher rate among diabetic patients receiving oral therapy. However, further analysis of the data reveals that the three treatment groups were dissimilar in age ($P = 0.074$) and sex distribution ($P = 0.02$) (Table V).

Discriminant analysis was performed to determine which linear function of age, sex and treatment regimen best differentiated between the survivors and nonsurvivors of acute myocardial infarction. This multivariate technique allows one to control for age and sex before examining the contributions of the treatment variables to mortality. The discriminant function (D) ($P < 0.05$) obtained was: D* = 928.5 − 14 (age) + 12 (male) − 12 (female) − 71 (insulin) − 47 (oral therapy) + 118 (diet). After adjustment for age and sex, the difference among

* (Holds only for 34 < age < 89 and scaled so that a positive D indicates a greater likelihood of survival.)

TABLE I

Type of Oral Hypoglycemic Agent in 151 Cases

	Patients (no.)
Tolbutamide	63
Chlorpropamide	33
Tolazamide	6
Acetohexamide	7
Phenformin	9
Tolbutamide + phenformin	7
Chlorpropamide + phenformin	6
Tolazamide + chlorpropamide	2
Chlorpropamide + phenformin	1
Tolbutamide + tolazamide	1
Tolbutamide + chlorpropamide + phenformin	1
Not specified	15
Total	151

TABLE II

Fourteen Cases of Primary Ventricular Fibrillation: Diabetic Treatment on Admission

Days After Admission	Therapy	Outcome
12	Chlorpropamide	Died
22	Chlorpropamide	Died
1	Diet	Died
1	Chlorpropamide	Died
12	Diet	Died
10	NPH insulin, 40 μ	Survived
5	NPH insulin, 28 μ	Died
16	Chlorpropamide + phenformin	Died
1	Tolbutamide	Died
5	Acetohexamide	Died
8	Tolbutamide	Died
7	Tolbutamide	Died
20	Tolbutamide	Died
13	Tolbutamide	Died

TABLE III

Incidence of Primary Ventricular Fibrillation (VF) by Type of Diabetic Management

Management of Diabetes	Total Patients	Patients With VF	
		no.	%*
Diet only	60	2	3.3
Insulin	54	2	3.7
Oral drugs	151	10	6.6
Total cases	265	14	5.3

* Chi square = 1.36 (not significant).

TABLE IV

Mortality by Type of Diabetic Management

Management of Diabetes	All Patients	Patients Who Died	
		no.	%*
Diet only	60	10	16.7
Insulin	54	14	25.9
Oral drugs	151	40	26.5
Total cases	265	64	24.2

* Chi square = 2.58 (not significant).

TABLE V

Summary of Age and Sex Distributions by Type of Diabetic Management

	Diet Only	Insulin	Oral Drugs
Patients (no.)	60	54	151
Mean age (yr)	62.3	62.6	65.5
Standard deviation	11.4	12.0	10.4
Standard error	1.5	1.6	0.9
Percent male	72	50	70

the three treatment regimens did not reach the $P < 0.05$ level, although patients receiving insulin and oral therapy had a lesser likelihood of survival.

There was no significant difference in the incidence of primary ventricular fibrillation or mortality when the data were reexamined for the sulfonylurea drugs alone. No apparent difference was noted between the type of diabetic management and the site of myocardial infarction.

Discussion

In 1974 Solar et al.[6] suggested that diabetic patients taking oral hypoglycemic agents had a greater incidence of primary ventricular fibrillation after myocardial infarction. This study also was followed by statements of support[7] and criticism.[8–10] These criticisms pointed out the small size of the study (184 patients), the effect of insulin which was administered after admission and the lack of distinction between sulfonylureas and phenformin. Our study revealed a trend toward increased occurrence of primary ventricular fibrillation in patients with either type of oral hypoglycemic agent, but the overall rate was too small to detect a statistically significant difference with our sample size. Assuming a rate of 3.5 percent among patients treated with diet alone or insulin, 386 records of patients receiving oral drugs would have had to have been reviewed to be sure at a 90 percent confidence interval that a rate twice the control level was not missed by chance. The significance of the slightly greater mortality in the group receiving oral hypoglycemic agents could not be determined in our study since variables such as time of onset and severity of diabetes were unknown.

Inotropic and chronotropic effects of oral hypoglycemic agents: In vitro studies[11] indicating that sulfonylureas exert an inotropic effect on the myocardium and increase the automaticity of Purkinje fibers were cited as possible explanations of Soler's findings. Other in vitro studies[12] using human papillary muscle preparations showed no inotropic effect and no evidence of potentiation of the inotropic effect of norephinephrine by tolbutamide. Wu et al.[13] have shown decreasing left ventricular function in diabetic animals taking tolbutamide and evidence of accumulation of periodic acid-Schiff staining material in the interstitium. In human subjects, Young et al.[14] found no significant inotropic effects immediately after infusion of tolbutamide but did note a significant effect 5 to 10 minutes later that might have been due either to tolbutamide or to increased insulin levels at that time. Hildner[15] noted a positive inotropic effect lasting for 30 minutes after a bolus injection of 250 mg of tolbutamide in patients during cardiac catheterization, but he found no obvious chronotropic effects or any change in automaticity. The interval of several days between the last dose of oral hypoglycemic agent and the episode of ventricular fibrillation in most of our patients makes a direct inotropic or chronotropic effect unlikely.

The mortality associated with episodes of ventricular fibrillation in our series was greater than that reported by others.[16] An increased mortality in diabetic patients with cardiovascular disease has been noted in the Framingham population[17] and is not thought to be entirely explained by the associated risk factors frequently found in diabetic patients. There is insufficient evidence from our study to conclude that there is a significant relation between primary ventricular fibrillation and the method of diabetic therapy.

Acknowledgment

We gratefully acknowledge the work of our clinical epidemiology technicians, Mrs. Biruta J. Schroeder, MA, and Ms. Anne-Marie Kunzler, MA, and thank Mrs. Edith Erick and Mrs. Frances Schlesinger for their secretarial assistance.

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Influence of Dobutamine on Hemodynamics and Coronary Blood Flow in Patients With and Without Coronary Artery Disease

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The influence of dobutamine on hemodynamics and coronary blood flow was studied in patients after routine cardiac catheterization. The data demonstrated that dobutamine is a powerful inotropic agent at a dose that has a relatively small influence on heart rate. In patients without coronary artery disease dobutamine greatly increased coronary arterial perfusion. In patients with severe coronary artery disease dobutamine resulted in a much smaller increase in coronary perfusion, and the pattern of perfusion became more inhomogeneous. The results suggest that dobutamine has a potential inotropic value but raise concern about its influence on regional myocardial perfusion in patients with serious coronary artery disease.

The search for the ideal inotropic agent for the management of acute cardiac depression and shock of any origin, particularly that due to myocardial pump failure, continues to be a therapeutic challenge. Dobutamine has recently been developed by Tuttle et al.[1] in an attempt to provide an inotropic agent that increases myocardial contractility and coronary blood flow while producing relatively little change in heart rate, heart rhythm or peripheral vascular resistance. In addition, experimental studies have suggested that dobutamine may limit infarct size.[1]

If dobutamine could increase contractility without markedly altering heart rate and could also increase coronary blood flow significantly and uniformly without introducing a regional myocardial imbalance between oxygen demand and availability, it would be a very useful therapeutic agent. Accordingly, this study was performed to evaluate the influence of dobutamine on hemodynamics and regional myocardial blood flow in patients with and without coronary artery disease. It represents an extension of our previous animal investigation,[2] which suggested that under certain circumstances dobutamine increases the extent of myocardial injury in anesthetized dogs with acute coronary occlusion.

Methods

Eighteen patients undergoing cardiac catheterization and coronary arteriography were studied; informed consent for diagnostic cardiac catheterization and for the dobutamine study was obtained from each patient. Mean systemic arterial pressure, maximal first derivative of left ventricular pressure (dP/dt), left ventricular end-diastolic pressure (18 patients), cardiac output (12 patients) and regional myocardial perfusion (8 patients) were measured 20 minutes after completion of the diagnostic catheterization procedure. These same measurements were repeated in all patients after a 5 minute infusion of dobutamine at a rate of 8 μg/kg per min and again in five of these patients after an additional 5 minute infusion of 15 μg/kg per min of dobutamine.

All pressures were measured with Statham P23Db pressure transducers and recorded on an Electronics for Medicine photographic recorder. The left ventricular recording system had a natural frequency of 18 hertz. Left ventricular dP/dt was obtained with a circuit that was linear within 5 percent to a frequency of 37 hertz.

Myocardial blood flow was determined by the method of Kety et al.,[3,4] using xenon-133 as the diffusible indicator; 15 to 18 mCi of the indicator dissolved in

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less than 2 ml of sterile pyrogen-free solution was injected over approximately 2 seconds through a catheter in place in the main left coronary artery. The injection was immediately followed by a saline flush, and the catheter was then withdrawn from the coronary orifice. The myocardial perfusion study was accomplished with a large crystal scintillation camera interfaced to a data acquisition system (Nuclear-Chicago pho/gamma III camera, Ohio-Nuclear 150 data system). The gamma radiation emitted by ^{133}Xe in myocardial cells was recorded in the form of consecutive frames of 3.6 seconds' duration, and these data were stored in a 64 by 64 matrix.

Calculation of myocardial flow was performed using exponential curve fitting by the weighted least squares method to the first 36 seconds of the ^{133}Xe washout curves. The ^{133}Xe image was visualized by displaying the content of each frame serially upon an oscilloscope. Regional flow values were generated from within the entire ^{133}Xe image and selected so that each value calculated represented a square of myocardium measuring 1.6 cm to a side. The effective resolution of our camera with a high resolution collimator imaging a beating heart is about 1 cm. This empirical resolution limit includes the image-degrading effects of Compton scatter. The choice of 1.6 cm squares as regions of interest was based on considerations of resolution and good counting statistics. Maximal total count rate during the coronary flow measurements never exceeded 8,700 counts/sec. With a system dead time of 10 μsec, this could not have caused appreciable image distortion or an unreasonable count rate error due to dead time.

Coronary arteriography and flow studies: The studies in which coronary blood flow were measured were accomplished with the patient lying supine on a floating tabletop. The collimator of the gamma camera was positioned at the head of the table so that when the patient was moved underneath the camera, the collimator bore the same relation to the heart as the cineangiographic camera. This procedure allowed accurate and reproducible positioning for both angiographic and imaging studies, which would have been difficult if the patient had been in an oblique position instead of lying supine. Three radiopaque markers were placed on the external chest wall over the precordium during coronary angiography and the location of the three points identified with an isotope marker after each myocardial perfusion study. This technique permitted superimposition of the arteriographic and flow studies and also allowed detection (and correction of) any slight positional difference that might have occurred between the two flow studies. It also made it possible to demonstrate certain results by superimposing values of local myocardial perfusion rates onto tracings of the posteroanterior coronary angiograms (see Results section and Fig. 4 and 6 to 9). Others[6] have also used this method to demonstrate regional coronary blood flow in patients.

Although the procedure permits a graphic presentation of angiographic and flow results, one cannot assume that the value of a given area exclusively represents perfusion of the coronary segment superimposed upon the area. For example, the anterior and posterior walls of the heart are estimated to be about 4 and 8 cm, respectively, from the collimator face. If these distances are considered a point source and the inverse square law is applied, with consideration of the mass attenuation coefficient for ^{133}Xe in muscle (0.178),[7] then approximately 13 percent of the total activity detected arises from the 8 cm source. In the frontal projection used the contribution of the circumflex circulation to the total perfusion value was obviously minimal. However, we believe that this method permits accumulation of meaningful coronary blood flow data, especially in relation to changes in absolute coronary flow after an intervention such as the administration of dobutamine; the method also allows one to assess regional homogeneity of coronary flow using each patient as his own control.[8]

Cardiac output was measured by injecting 8 mg of indocyanine green dye into either the pulmonary artery or the

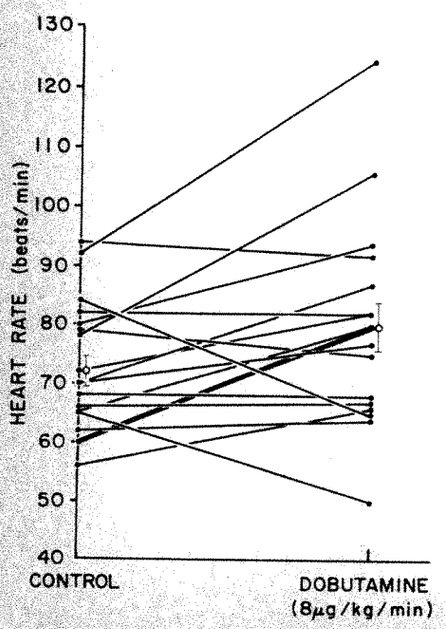

FIGURE 1. Changes in heart rate after infusion of dobutamine (8 μg/kg per min) in 18 patients. Each dot represents an individual patient. The **open circles** represent the mean change ± standard error for all 18 patients.

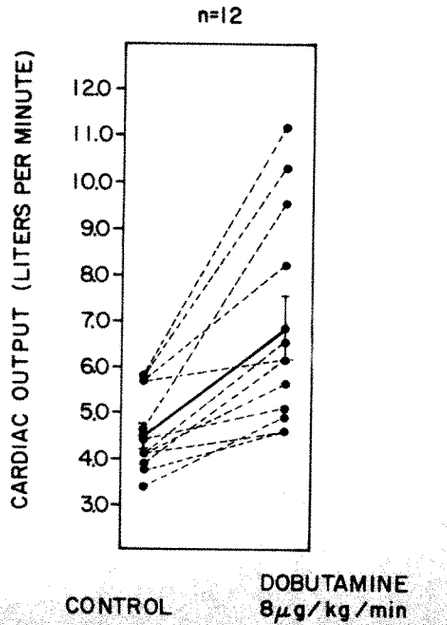

FIGURE 2. Changes in cardiac output after infusion of dobutamine (8 μg/kg per min) in 12 patients. The **solid line** demonstrates the mean increase in cardiac output after infusion of dobutamine in the patients studied.

superior vena cava with sampling from the left brachial artery using a cardio-densitometer (Beckman Instruments, Inc., Spinco Division, Palo Alto, Calif.).

Paired t test comparisons were made in each patient between control values for each variable and the corresponding value after dobutamine. The results were considered significant when $P < 0.05$.

Results

Eighteen patients (nine male, nine female) were studied; the mean age for the groups was 46 years. Nine patients had significant coronary artery disease; five of these had diffuse, severe three vessel disease, three had severe obstruction of the proximal left anterior descending coronary artery and one had marked narrowing of the main left coronary artery. Of the nine patients without significant coronary obstruction three had rheumatic mitral valve disease and six had chest pain of uncertain origin but normal coronary arteries.

Hemodynamics

Heart rate: The infusion of 8 μg/kg per min of dobutamine was associated with an increase in mean heart rate of 10 percent (72 ± 2.6 [standard error] to 80 ± 4.1 beats/min, $P < 0.05$) (Fig. 1). In the five patients given dobutamine at a rate of 15 μg/kg per min heart rate increased 27 percent over the preinfusion value. There was no increase in ventricular premature beats during the infusion of dobutamine at either dose and no patient had a sustained atrial or ventricular rhythm disturbance.

Cardiac output: This value, measured in 12 patients, increased by 52 percent (4.5 ± 0.27 to 6.8 ± 0.67 liters/min, $P < 0.001$) during administration of dobutamine at a rate of 8 μg/kg per min (Fig. 2). This increase in cardiac output was at least partly independent of the increase in heart rate since it also occurred in the six patients whose heart rate did not change significantly after this dose of dobutamine. Cardiac output was not measured in the five patients who received 15 μg/kg per min of dobutamine. Each patient who received the dose of 8 μg/kg per min of dobutamine showed a significant increase in stroke volume, stroke volume increasing in the group by 45 percent from 65 to 95 ml/min ($P < 0.01$).

Arterial pressure: A dose of 8 μg/kg per min of dobutamine was associated with a 25 percent increase in systemic mean arterial pressure (82 ± 4.4 to 103 ± 5.9 mm Hg, $P < 0.001$) (Fig. 3). There was no further significant increase in arterial pressure after infusion of 15 μg/kg per min in the five patients who received this additional dose.

Myocardial contractility: A dose of 8 μg/kg per min of dobutamine was associated with a significant increase in contractility as judged by an increase of 128 percent in maximal left ventricular dP/dt (1,595 ± 122 to 3,369 ± 260 mm Hg/sec, $P < 0.001$) (Fig. 4). There was a further 200 percent increase in this value to 4,832 mm Hg/sec ($P < 0.01$) in the five patients who received 15 μg/kg per min of dobutamine.

Regional Myocardial Perfusion

Quantitation of regional myocardial perfusion was accomplished in eight patients. Three of these patients had normal coronary arteries, three had severe diffuse triple vessel coronary artery disease and two had severe proximal isolated left anterior descending coronary arterial stenosis.

During the infusion of dobutamine at a rate of 8 μg/kg per min the three patients with normal coronary arteriograms had a 137 percent increase in perfusion; moreover, the pattern of regional myocardial perfusion

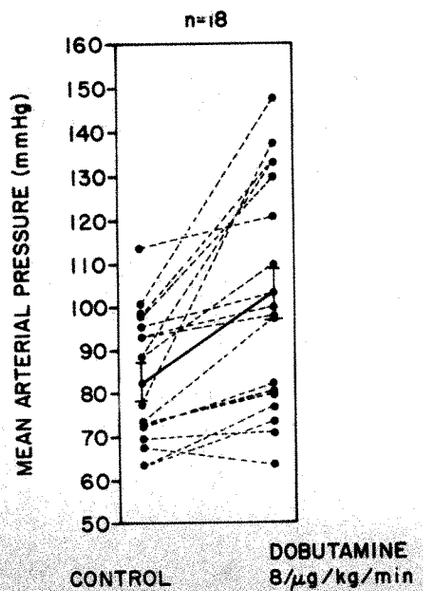

FIGURE 3. Changes in mean arterial pressure after infusion of dobutamine. Format as in Figure 2.

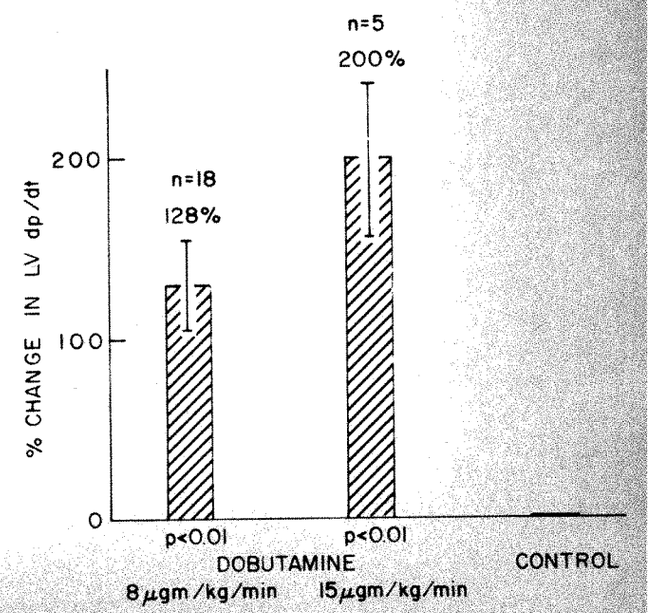

FIGURE 4. Changes in left ventricular dP/dt after infusion of dobutamine at rates of 8 (18 patients) and 15 (5 patients) μg/kg per min.

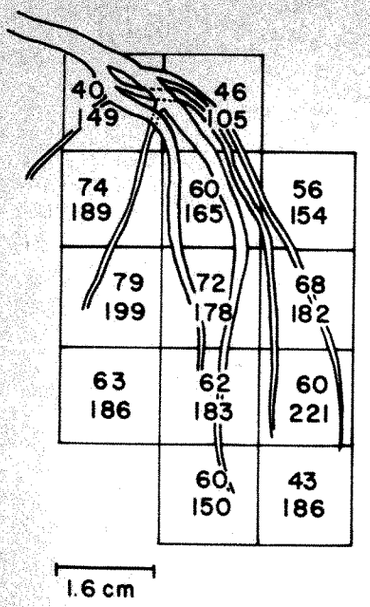

FIGURE 5. Example of the marked increases in regional myocardial perfusion (superimposed over a line drawing of the left coronary system) observed after infusion of dobutamine in patients without significant coronary artery disease. The top figure in each box represents the coronary blood flow in ml/min per 100 g left ventricle before infusion of dobutamine; the bottom figure in each box represents flow after dobutamine. Note the marked generalized increase in coronary flow that occurred after infusion of the drug.

became more homogeneous (Fig. 5 and 6). In contrast, the three patients with significant three vessel coronary artery disease had an overall increase in perfusion of only 24 percent. In addition, two of the three subjects exhibited a more heterogeneous pattern of regional perfusion during infusion of dobutamine (Fig. 6 to 9).

In the two patients whose coronary arterial stenosis was confined to the proximal left anterior descending vessel the increase in perfusion after dobutamine ap-

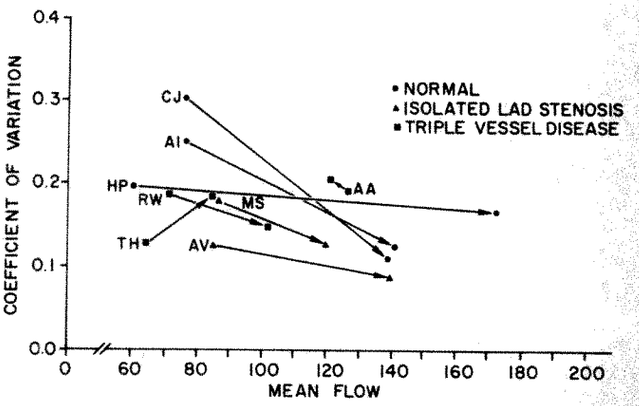

FIGURE 6. Comparison of mean regional flow and homogeneity of regional flow before and after infusion of dobutamine in eight patients. The ordinate scale represents the coefficient of variation of regional flow, an index of regional flow heterogeneity. The only two patients in whom flow heterogeneity increased with dobutamine had severe three vessel disease; the greatest decreases in heterogeneity occurred in normal subjects. LAD = left anterior descending coronary artery.

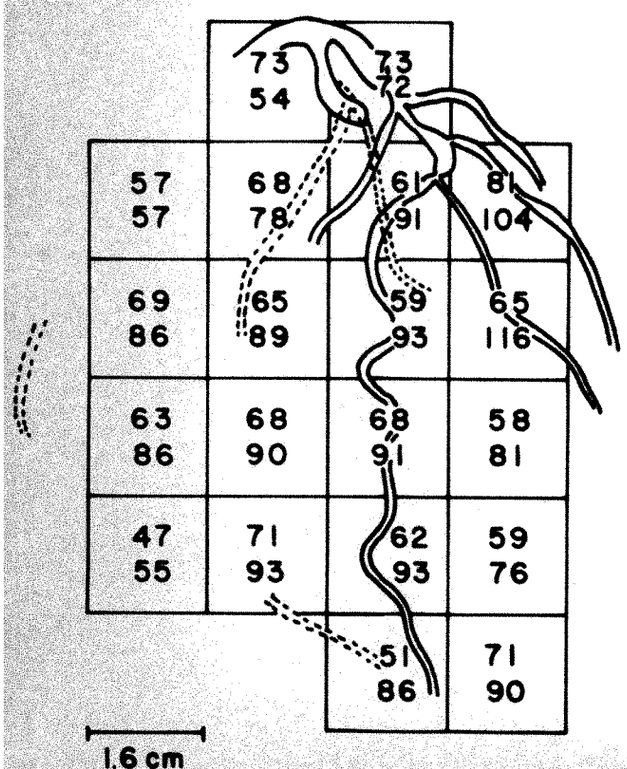

FIGURE 7. Relatively small increases in coronary flow after infusion of dobutamine in a patient with severe three vessel coronary artery disease. Format as in Figure 5 with the addition of demonstration of the sites of severe coronary narrowing.

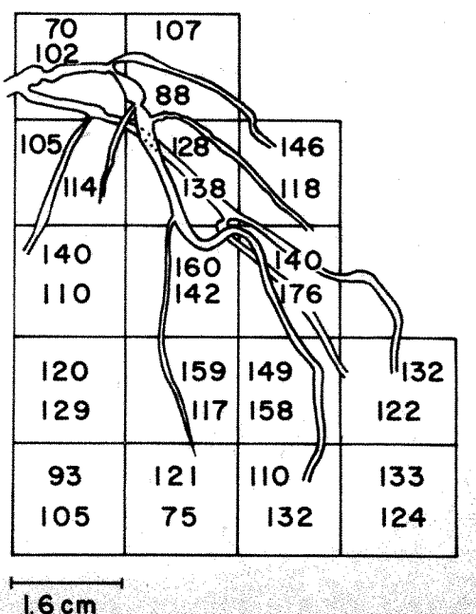

FIGURE 8. Coronary flow changes after infusion of dobutamine in a second patient with severe three vessel coronary artery disease. Format as in Figure 7. Note that there are some areas in which flow decreased after dobutamine.

peared to be intermediate between that noted in patients with severe three vessel disease and in those with normal coronary arteries (Fig. 6 and 10). The increase in left ventricular perfusion in these patients was 47 percent.

Discussion

Inotropic effect of dobutamine: The data obtained in this study suggest that dobutamine may have some advantages over certain other inotropic agents. It increases myocardial contractility and cardiac output but has a relatively small effect on heart rate. Eight μg/kg per min of dobutamine increased cardiac output by 52 percent, mean arterial pressure by 25 percent and maximal left ventricular dP/dt by 128 percent; the increase in heart rate was only 10 percent. The increase in mean arterial pressure after dobutamine makes it somewhat more difficult to assess dobutamine's influence on contractility, but the increase in left ventricular dP/dt after dobutamine cannot be adequately explained by the increase in mean arterial pressure either in individual patients or in the group as a whole. In addition, dobutamine has been shown to exert a marked inotropic effect in experimental animals at a time when no significant change in mean arterial pressure occurred.[2] In this study the administration of dobutamine was not associated with frequent ventricular premature beats, and there was no sustained atrial or ventricular rhythm disturbance. Dobutamine's tendency to increase heart rate, and to some extent arterial pressure, has previously been shown to be limited in experimental animals by reflex vagal cardiac slowing and withdrawal of peripheral sympathetic tone, which are stimulated by the increase in arterial pressure that dobutamine produces.[9] In experimental animals dobutamine, in doses equi-inotropic to isoproterenol, may produce less increase in myocardial oxygen consumption in that it has a less marked effect on heart rate and arterial pressure than does isoproterenol.[9,10] Equi-inotropic doses of norepinephrine, epinephrine and dopamine caused greater pressure responses than dobutamine, again costly in terms of myocardial oxygen consumption.[10] Dopamine also had a greater chronotropic effect than dobutamine at similar inotropic levels, also adversely increasing myocardial oxygen consumption.[10]

Effect on myocardial performance: In this study dobutamine at a rate of 8 μg/kg per min produced a generalized and marked increase in myocardial perfusion in patients without coronary artery disease. However, in patients with severe three vessel coronary artery disease dobutamine caused a much smaller increase in coronary blood flow. This same phenomenon has been noted previously in our laboratory with the potent inotropic agent isoproterenol.[11] In contrast to the three normal patients whose regional perfusion became more homogeneous with infusion of dobutamine, two of the three patients with three vessel disease exhibited a more inhomogeneous perfusion pattern after administration of dobutamine, as indicated by the increased coefficient of variation in Figure 6. This limited increase in coronary flow in the setting of severe coronary artery disease, coupled with dobutamine's marked positive effect on contractility, suggests a potentially deleterious effect in patients with extensive coronary artery disease. Patients with single vessel coronary disease also had a smaller increase in regional myocardial perfusion after dobutamine than did normal subjects; their response

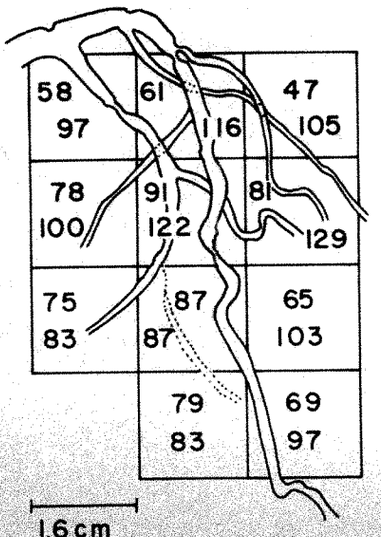

FIGURE 9. Coronary flow changes after infusion of dobutamine in the third patient with severe three vessel coronary artery disease.

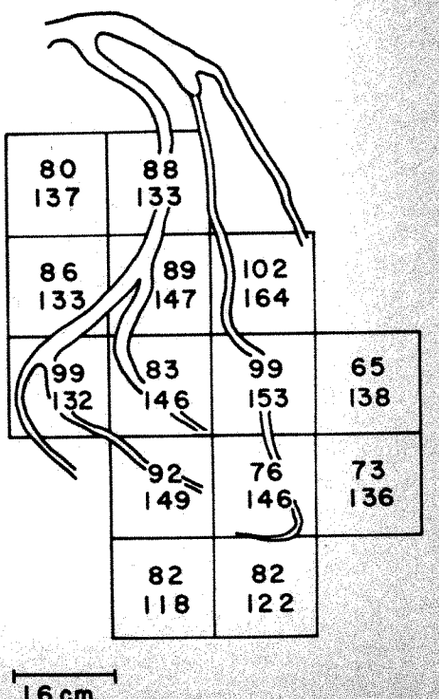

FIGURE 10. Representative example of the coronary flow changes after dobutamine in a patient with severe narrowing of only the proximal left anterior descending coronary artery.

appeared to be intermediate between that noted in patients with severe, diffuse coronary disease and that noted in normal subjects.

The results obtained in this study are supported by our previous observations in experimental animals.[2] At infusion rates of 4 to 20 μg/kg per min dobutamine significantly increased heart rate, contractility (left ventricular dP/dt and dP/dt/P [maximal rate of rise of left ventricular pressure divided by developed pressure during systole]) and regional myocardial flow during acute myocardial ischemia in anesthetized dogs and during chronic myocardial ischemia and infarction in awake, unsedated dogs. In anesthetized dogs with acute myocardial ischemia dobutamine at a rate of 20 μg/kg per min increased epicardial S-T segment elevation, suggesting its potential to extend myocardial damage in this setting when heart rate and contractility were also significantly increased.

Clinical implications: Our data demonstrated that dobutamine is a powerful inotropic agent in patients even at doses at which it exerts a relatively small effect on heart rate. The number of patients studied was small, but dobutamine also appeared to increase myocardial perfusion significantly in patients without coronary artery disease while producing much smaller increases in mean coronary blood flow and possibly further increasing the inhomogeneity of regional coronary perfusion in at least some patients with severe coronary artery disease. These findings suggest that dobutamine should be used with caution in patients with severe coronary artery disease but can increase contractility in the setting of myocardial depression not associated with extensive coronary artery disease.

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Mitral Valve Malformation of Ebstein Type in Absence of Corrected Transposition

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The first documented case is reported of mitral valve malformation of the Ebstein type in the absence of corrected transposition. In this case, the ring of the inferior leaflet of the mitral valve was displaced downward into the left ventricle, dividing the latter into a proximal atrialized and a distal effective ventricular chamber. The anterior leaflet was not displaced. The chordae tendineae of both leaflets were thickened. The papillary muscles were hypertrophied and abnormal in architecture. The outflow tract of the effective left ventricle was shortened. The valve leaflets were thickened, and the mitral valve was probably insufficient.

In 1866 Ebstein described an unusual abnormality of the tricuspid valve in which the valve leaflets were fused and displaced into the right ventricular cavity.[1,2] This displacement of the tricuspid valve into the right ventricle may result in various degrees of tricuspid insufficiency, tricuspid stenosis and cyanosis. Ebstein's malformation may also occur in corrected transposition of the great vessels with ventricular inversion and involvement of the tricuspid (left) atrioventricular (A-V) valve.[3-9] The result is clinical "mitral insufficiency." There are no documented instances of a malformation of the Ebstein type involving the true mitral valve. For this reason, we report herein the cardiac anatomic features of a patient with this anomaly.

Case Report

A newborn infant boy was born after 1.5 hours of uncomplicated labor to a gravida I, para I 17 year old woman who had virtually no prenatal care. The infant weighed 3.3 kg and had an Apgar score of 1 at 1 minute. He required resuscitative measures including endotracheal intubation. No further problems were recognized until he was 12 hours old when signs of cyanosis and respiratory distress developed. A chest roentgenogram (Fig. 1) was interpreted as demonstrating cardiomegaly with increased pulmonary vascular markings. An electrocardiogram was not obtained. Arterial blood gas values were: oxygen tension (PO_2) 58 and carbon dioxide tension (PCO_2) 28 mm Hg and hydrogen ion concentration (pH) 6.95. At age 30 hours the infant was transferred to the Geisinger Medical Center. He was definitely cyanotic and had congestive heart failure. The pulse rate was 140 beats/min and the respiratory rate 80/min. Subcostal and intercostal retractions were noted. Moist rales were diffusely present. The liver was enlarged and palpable down to the level of the umbilicus. The brachial and femoral pulses were equal but weak. A systolic thrill was present over the entire left precordium. The first heart sound was normal; the second sound was definitely split but not abnormally accentuated. A grade 3 pansystolic murmur was heard all over the precordium but was loudest at the left lower sternal border. No diastolic murmurs were noted. Digitalis, meralluride (Mercuhydrin®) and sodium bicarbonate were administered, but the infant died 5 hours after the transfer.

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Pathologic Examination

Aside from the findings in the heart, the pathologic diagnoses were chronic passive hyperemia of the lungs, liver and spleen, pulmonary edema and hemorrhage.

The heart was somewhat enlarged, weighing about 25 g (expected weight 16 g). External inspection of the left atrium and ventricle clearly revealed the A-V sulcus demarcating these chambers. The left ventricle was divided into two parts. The proximal portion of this chamber was paper-thin and clearly demarcated from the distal portion (Fig. 2). From the base of the heart the great vessels emerged with a normal relation; a somewhat enlarged pulmonary artery was anterior and to the left of a smaller aorta.

The right atrium was enlarged and thickened. An atrial septal defect of the fossa ovalis type measured 0.8 cm at its greater diameter (Fig. 3). The tricuspid orifice was somewhat enlarged, but the valve was normally formed. The coronary sinus was flattened but patent. The right ventricle was hypertrophied and enlarged. Its architecture was normal. A normal pulmonary artery arose from this chamber. A widely patent ductus arteriosus led into the descending aorta.

The left atrium (Fig. 4) was greatly enlarged. Its wall was paper-thin in areas. The pulmonary veins entered it in a normal manner. The inferior mitral valve leaflet and the mitral valve orifice were displaced downward into the left ventricle, dividing that chamber into a proximal atrialized and a distal ventricular chamber (Fig. 4 and 5). The aortic leaflet was not displaced. The edges of both leaflets were thick and nodular. The attachments of the valve were abnormal. Two groups of stocky short papillary muscles originated close to the apex. They were attached to the anterior and posterior leaflets by short relatively thick chordae tendineae (Fig. 4 and 5). The mitral valve orifice was slightly smaller than normal (Fig. 4).

The proximal left ventricular chamber was paper-thin. Its endocardium was thin proximally but thick distally. The distal left ventricular chamber was smaller than normal, especially in the outflow region, and its wall was thinner than normal for a left ventricle of this age. The ventricular septum was thinned out and outpouched toward the right (Fig. 5). The wall was spongy and trabeculated. The aorta and its valve appeared normal.

The coronary arterial circulation was normal and of the dominant left type.

Discussion

The diagnosis of the lesion of the mitral valve was made on the basis of identification of the left A-V sulcus, which was demarcated by the left circumflex coronary artery passing through this region. Thus, the effective inferior mitral leaflet was displaced downward into the left ventricle, subdividing that chamber into an atrialized proximal chamber separated by the mitral valve from the effective left ventricle—the distal chamber. The papillary muscles were abnormal. These features merit the diagnosis of malformation of the mitral valve of the Ebstein type.

To our knowledge, this is the first documented case of this malformation. Only Becu et al.[5] have previously referred to this type of heart. They note that one of their group examined a heart in another collection that "had a basically normal configuration but which also had one feature of the Ebstein-type of malformation in the mitral valve. In it, the posterior leaflet of the mitral valve had a basal attachment to the left ventricular wall inferior to the mitral annulus fibrosis but the lower edge of the mitral valve was not abnormally attached."

The mitral valve in our case was probably insufficient. The left atrium was huge and the right side of the heart was hypertrophied. At birth, the infant required resuscitation and later had signs of congestive heart failure with tachypnea and cyanosis. There was probably a left to right shunt through the atrial septal defect.

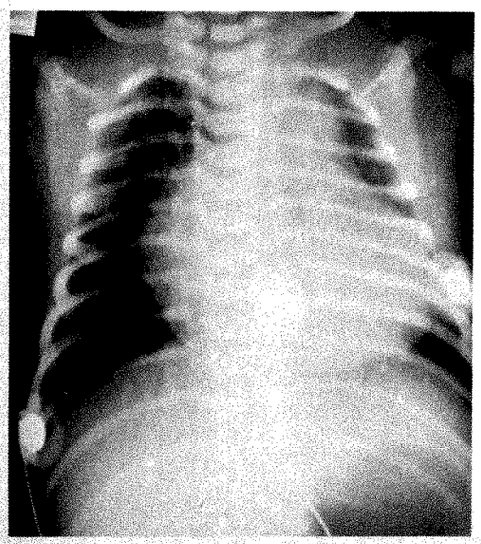

FIGURE 1 (top). Chest roentgenogram.

FIGURE 2 (right). External examination of part of the left atrium and ventricle. AV = atrioventricular sulcus; DVC = distal ventricular chamber; LA = left atrial wall; PVC = proximal ventricular chamber.

Embryogenesis: The embryogenesis of this anomaly is obscure. Normally,[10] the left A-V (mitral) orifice at developmental stage 10 to 12 mm, is surrounded medially by the tubercles of the anterior and posterior endocardial cushions and laterally by the left lateral cushion. A subsequent process of undermining of the muscle of the developing left ventricle joins muscular tissue to the endocardial cushion tissue to form four completely divided compartments, two anterior and two posterior. These compartments, consisting of endocardial tissue and muscle, form valves, chordae tendineae and papillary muscles. The junction of the adjacent anterior and posterior components both medially and laterally results in the medial aortic leaflet of the mitral and lateral (posterior, inferior) leaflet and the anterior and posterior papillary muscles. We may theorize that in our case there was an abnormality in the formation or placement of the left lateral endocardial cushion.

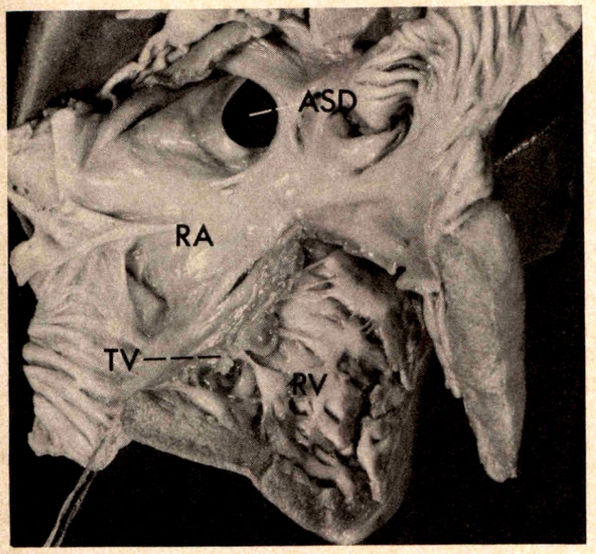

FIGURE 3 (top). Right atrial and right ventricular view. ASD = atrial septal defect, fossa ovalis type; RA = right atrium; RV = right ventricle; TV = tricuspid valve.

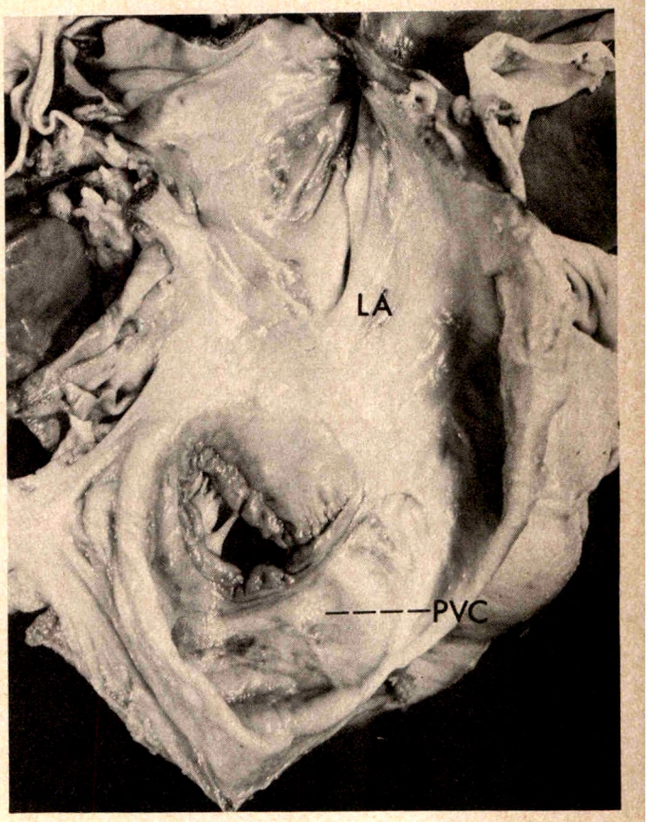

FIGURE 4 (right). View of left atrium (LA), mitral valve and proximal ventricular chamber (PVC).

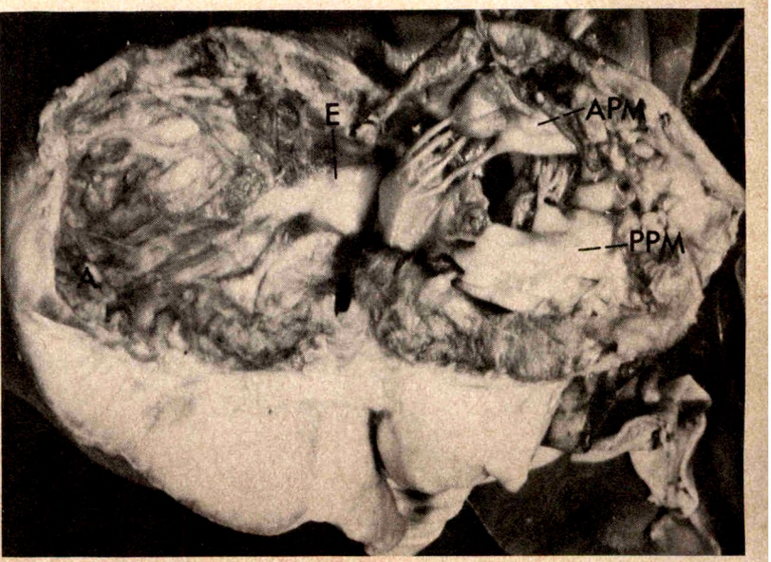

FIGURE 5. Distal ventricular chamber. A = artifact (a cut had been made in the ventricular wall); APM = anterior papillary muscle; E = endocardial surface; PPM = posterior papillary muscle.

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Surgical Correction of Truncus Arteriosus in Infancy

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An 8 week old infant with severe heart failure from type 1 truncus arteriosus underwent successful corrective surgery employing the Rastelli procedure with use of deep hypothermia and total circulatory arrest. Postoperative hemodynamic studies showed complete closure of the septal defect, disappearance of truncal stenosis, but presence of mild porcine valve stenosis. This procedure is possible even in very small subjects and is preferable to palliative pulmonary arterial banding.

Truncus arteriosus is a rare cardiac anomaly characterized by a single arterial trunk emerging from the heart and supplying the coronary, systemic and pulmonary circulations. In 1967, Rastelli developed a technique for its correction using an aortic homograft with its adjoining mitral valve.[1] Previously, the defect was generally considered uncorrectable although implantation of a valveless cloth tube conduit from the right ventricle to the pulmonary artery has been performed.[2] Palliative pulmonary arterial banding was often tried in cases with excessive pulmonary flow, but results were generally poor. In recent years, a modification of the Rastelli procedure using a prosthetic conduit with a valve attached[3,4] has been successfully performed in children aged 13 months to 18 years. This communication describes an infant with truncus arteriosus who underwent surgical correction with this technique at age 5 weeks.

Case Report

The infant was male, the product of a full term uncomplicated pregnancy and normal vaginal delivery. He was reported to be normal at birth and did well until the age 8 weeks when respiratory distress developed and he was admitted on March 23, 1974 with congestive heart failure. Physical examination revealed mild cyanosis and moderate respiratory distress; weight was 4.2 kg, blood pressure 90/60 mm Hg, pulse rate 150/min and respirations 60/min. Cardiac examination revealed 2+ right and left ventricular impulses and a systolic thrill over the left sternal border. The first heart sound was normal and was followed by a systolic ejection click along the left sternal border. The second sound was single and loud. A grade 4/6 medium-pitched long systolic murmur heard all over the precordium was most prominent over the third left intercostal space. A grade 2/4 short mid-diastolic rumble was heard at the apex. Examination of the lungs revealed fine moist rales at both bases. The peripheral pulses were normal initially but became bounding after digitalization. The liver edge extended down to 4 cm below the right costal margin.

Laboratory studies revealed the following values: hemoglobin 15.3 g/100 ml, hematocrit 44.6 percent, white blood cell count 14,300 mm^3 with normal differential; platelet count 198,000. Urinalysis was normal. Chest roentgenograms revealed marked cardiomegaly and increased pulmonary vasculature. The electrocardiogram and vectorcardiogram revealed a frontal QRS axis of +45° and severe left ventricular hypertrophy.

Course: The infant was treated with digitalis, diuretic agents and oxygen. Fluid intake and output and arterial pH and gases were monitored. Cardiac catheterization was performed 4 days after admission. A systolic pressure gradient of 10 to 15 mm Hg between either ventricle and the common trunk was

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present (Table I). Biplane cineangiocardiograms obtained with selective injection of contrast medium into the right ventricle, left ventricle and aortic root revealed a large cristal-type ventricular septal defect and abnormal arrangement of the great vessels typical of the truncus type I anomaly (Fig. 1). A patent foramen ovale was also present. Despite vigorous therapy, the infant's congestive heart failure progressed.

Corrective surgery: At age 8 weeks the infant underwent corrective surgery with use of deep hypothermia and circulatory arrest. The body temperature was lowered to 22° C by surface cooling and the cardiac anatomy identified. The trunk of the main pulmonary artery had a diameter approximately two thirds that of the ascending aorta. At 18° C, circulatory arrest was induced. A cristal type of ventricular septal defect, about 2 cm in its greatest diameter, was closed with a knitted Dacron® patch. The common trunk had three valve leaflets that appeared grossly normal. The pulmonary artery was excised from the common trunk and the aortic side closed with double continuous sutures. A 12 mm graft of woven Dacron with an attached porcine valve was anastomosed to the pul-

TABLE I

Hemodynamic Data

	Preoperative	Postoperative
Oxygen saturation (%)		
Right atrium	71	76
Right ventricle	81	78
Pulmonary artery	90	78
Left atrium	98	99
Aorta	91	99
Blood pressure (mm Hg)		
Right atrium	9/5(5)	10/9(6)
Left atrium	18/18(12)	12/18(10)
Right ventricle	105/9; 105/17*	60/9; 80/18*
Left ventricle	100/15	. . .
Pulmonary artery	75/30(45)	. . .; 55/20(35)*
Aorta	90/40(50)	100/40(60); 135/60(90)*
Cardiac index (liters/min per m^2)	5.3	8.6
Pulmonary-systemic shunt (Qp/Qs) (liters/min per m^2)	2.8	1.0
Pulmonary vascular resistance (dynes sec cm^{-5}/m^2)	203	224
Systemic vascular resistance (dynes sec cm^{-5}/m^2)	756	736

* Postangiographic recordings.

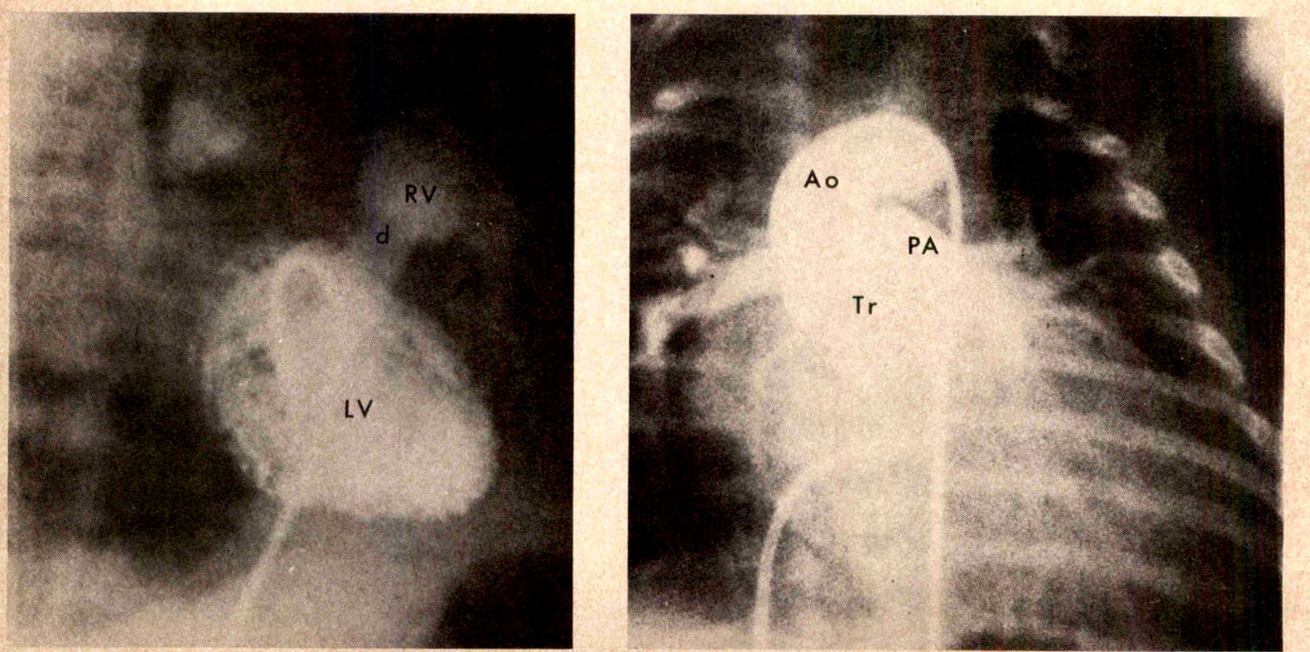

FIGURE 1. Preoperative biplane cineangiocardiograms. **Left,** lateral projection. Injection of contrast medium into the left ventricle, demonstrating large ventricular septal defect. **Right,** frontal projection. Injection into common trunk showing typical type 1 truncus. Ao = aorta; d = ventricular septal defect; LV = left ventricle; PA = pulmonary artery; RV = right ventricle; Tr = truncus arteriosus.

EDITORIALS

Computer Analysis of Echocardiograms

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In this issue of the Journal Saffer et al.[1] describe a technique for computer-aided analysis of echocardiograms. Given the rapid growth and interest in echocardiography, the application of computers to this diagnostic tool was predictable. As Saffer et al. state, many echocardiographic measurements and calculations are time consuming to perform. In addition, because some of these measurements vary with heart rate and respiration, averages of data from multiple cardiac cycles probably should be obtained. Such averaging obviously would be easier with the assistance of a computer.

Computers might also be used to obtain useful echocardiographic information that is not routinely obtained now because the manual calculations are too difficult. Such data might include the rate of change of left ventricular dimensions.[2] There is evidence that the rate of this change during diastole may be a sensitive indicator of left ventricular dysfunction.[3] Other measurements, including the time-distance area between valve leaflets, might provide useful hemodynamic information and would be much easier to determine with computer assistance. Thus, there is reasonable evidence to suggest that a computer could be helpful in obtaining some echocardiographic measurements now made manually and in deriving additional information from the recordings.

A variety of techniques have been proposed for computer analysis of echocardiographic information.[4–6] Several groups of investigators are trying to have the computer recognize certain echoes. Others are using gating systems that lock onto specific echoes. Both techniques have problems. Many echoes are close together and difficult to differentiate from each other. For example, the posterior left ventricular endocardium is frequently in apposition to structures from the mitral valve apparatus, and the motion of the echoes can be very similar. In many cases it would be almost impossible to gate solely on the endocardium and eliminate the mitral valve echoes. It might also be extremely difficult to program the computer to distinguish endocardial echoes from those of chordal structures.

The technique described by Saffer et al.[1] is similar in principle to that used by other investigators[2,5] and is based on a semiautomatic system in which the physician or technician identifies echoes and traces them using a digitizing pen with X and Y coordinates. Although this technique requires manual tracing of the echoes, time is saved because the computer performs the mathematical calculations. The system does not require a very sophisticated program and probably can be adapted to many computers now used in cardiac catheterization laboratories or other hospital units. The hardware is not much different from that used to determine ventricular volumes from left ventricular angiograms. Thus, this technique probably will be the most readily available method for introducing echocardiographic data into a computer.

Such a use of computers requires echocardiograms of high quality. A printed computer readout adds a certain unwarranted dignity to data, and there is no question that reports will be coming back with many calculations, some carried out to four or five significant figures. Yet, unless safeguards are provided, inadequate tracings may occasionally be used to make very sophisticated, but grossly inaccurate, measurements. I urge that anyone receiving computerized calculations of echocardiographic data also have the original echocardiograms available for scrutiny. In addition, he should be given some indication concerning the echoes selected for computer analysis.

Because of the ease with which computers can perform mathematic manipulations, echocardiographers may be tempted to make some unjustified calculations. For example, the calculation of echocardiographic left ventricular "volume" will undoubtedly appear on many computer readouts. As most experienced echocardiographers recognize, there are many limitations to this calculation and at best it provides a statistical estimate rather than a true measure of volume and only in certain patients. With the availability of a computer, calculations of left ventricular volumes and mass may be obtained for virtually every patient who has an echocardiographic study even though the formulas used may

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not be valid. Such calculations might impress many referring physicians not familiar with the limitations of echocardiography, but the inaccuracies could lead to serious patient mismanagement.

In summary, the expected increasing use of computers in echocardiography emphasizes the need for high quality echocardiographic recordings and cautious interpretation of mathematical manipulations of echocardiographic measurements. If these precautions are taken, computers should become a valuable adjunct to the analysis of echocardiographic data and improve the use of an important clinical tool.

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Antiarrhythmic Drugs: Changing Concepts

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Hypotheses on the mechanism of action of antiarrhythmic drugs are based mainly on studies of isolated normal cardiac tissue using the microelectrode technique.[1–4] In these studies, the effects of antiarrhythmic agents on variables including conduction, action potential duration and refractory period are determined and the results extrapolated to the in situ heart where they are fit into various hypothetical models of arrhythmogenesis. Classifications of antiarrhythmic agents are also based on such studies of normal isolated tissue,[5,6] although hearts with arrhythmias may have one or many abnormalities. There are limitations in this method of analysis[7,8] and, perhaps because of these limitations, the treatment of arrhythmias is to a significant degree empirical and not based on electrophysiologic principles or on any current classification of antiarrhythmic agents. In this editorial I will reexamine the ways in which antiarrhythmic drugs are studied and classified and discuss some work on in situ abnormal hearts that may help to determine the electrophysiologic properties of antiarrhythmic drugs in these hearts.

Tachyarrhythmias have been classified into the following categories: disturbances of impulse formation (automatic), disturbances of impulse conduction (primarily reentrant) and combinations of the two.[7,8] Automatic rhythms are generated when a cardiac cell or group of cells develop the capacity to fire at an increased rate. Reentry occurs when impulses encounter slowing of conduction and one-way block of antegrade conduction in a segment of diseased cardiac tissue.[7] Impulses then reenter the diseased segment in a retrograde direction completing the reentrant cycle. Boundary currents arising because of local differences between action potential durations in diseased and normal tissues may be an important cause of reentry.[8]

A major classification of antiarrhythmic agents separates them into two groups on the basis of in vitro studies.[5,6] Agents in group 1 (quinidine and procainamide, for example) have "local anesthetic" properties in slowing conduction and prolonging the action potential duration and the effective refractory period. In reentrant arrhythmias, these agents are thought to slow conduction to the point of block and to prolong refractoriness in the segment of one-way block, thus creating two-way block and interrupting the reentrant cycle.[7,8] Agents in group 2 (lidocaine and diphenylhydantoin, for example) are thought to have no effect on or to enhance conduction and thus may reverse one-way block by improving conduction in the previously blocked segment.[4,6] These agents shorten the action potential duration and the effective refractory period. Agents in both group 1 and group 2 depress automaticity at least in individual Purkinje fibers.[1,2] Propranolol has features of drugs in both groups; in isolated tissue, it tends to slow conduction and it shortens the action potential duration in Purkinje fibers but has no effect on or prolongs the action potential duration in ventricular muscle.[4]

Lidocaine in Acute Ischemia

Because this classification of antiarrhythmic drugs is based on studies of normal tissue in vitro and not on studies of abnormal hearts in situ its usefulness may be limited. It is thus a logical step to examine the electrophysiologic effects of antiarrhythmic drugs on abnormal regions of the heart and on the interplay between normal and abnormal tissue in situ. Such studies in canine models of myocardial ischemia and infarction have been undertaken to determine the effects of lidocaine and propranolol on conduction, action potential duration and effective refractory period in ischemic or infarcted and normal zones of the heart.[9–11] Since ventricular arrhythmias occur in acute ischemia, direct correlations were made in some of these studies between demonstrated antiarrhythmic properties and electrophysiologic effects.[10,11]

In dogs with 2 hour old myocardial infarction, lidocaine prolonged conduction and refractoriness in the infarcted but not in the normal zone of the heart.[9] In the first 15 minutes after coronary arterial ligation, lidocaine had antiarrhythmic effects in diminishing the frequency of ventricular beats[10] and while it had these effects it prolonged conduction and refractoriness only in the ischemic zone and it shortened the monophasic action potential duration only in the normal zone. Before the administration of lidocaine, the action potential duration was shorter in the ischemic zone than in the normal zone; with lidocaine this disparity was reduced.

Thus lidocaine had "local anesthetic" properties (that is, properties similar to those of quinidine) in slowing conduction and prolonging refractoriness in ischemic and infarcted zones of the heart in spite of its different

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effects in isolated normal tissue. Since reentry appears to be responsible for ventricular arrhythmias occurring during acute ischemia,[12] lidocaine may interrupt reentrant cycles by creating two-way block in the segment of tissue where there was previously one-way block; that is, the mechanism may be the same as that postulated for other local anesthetic agents. Other effects of lidocaine make transmission of impulses due to boundary currents less likely. Boundary currents may arise in acute ischemia because of the shorter action potential duration in the ischemic zone causing flow of depolarizing current and propagation of reentrant impulses from the normal to the ischemic zone.[8] Since lidocaine reduces the disparity between the action potential durations in these zones, the currents are less likely to occur. In addition, prolongation of refractoriness in the ischemic zone would cause impulses propagating from the normal to the ischemic zone to encounter more refractory tissue and to be less likely to propagate further.

Since lidocaine may slow conduction it should be used with caution in patients with ischemic heart disease because it could promote conduction abnormalities. Some clinical studies[13] have noted that lidocaine can cause such abnormalities to progress in certain of these patients.

Propranolol in Acute Ischemia

Like lidocaine, propranolol also had antiarrhythmic properties in reducing the frequency of ventricular beats during acute ischemia[11]; it slowed conduction only in the ischemic zone and prolonged the action potential duration and effective refractory period in the ischemic zone and to a lesser extent in the normal zone. Since propranolol prolonged the action potential duration more in the ischemic zone (where it had initially been shorter than in the normal zone) this drug considerably reduced the disparity between action potential durations in the two zones.

The slowing of conduction and prolongation of refractoriness induced by propranolol in the ischemic zone may have antiarrhythmic consequences similar to those postulated for lidocaine and other local anesthetic agents. Like lidocaine, propranolol reduces the disparity between action potential durations in the ischemic and normal zone, thus making boundary currents less likely. Interestingly, this effect of propranolol on action potential duration would have been difficult to determine by studying individual cells in isolated tissue baths. It is also of interest that lidocaine and propranolol have many similar electrophysiologic properties in the ischemic heart. The significance of these similarities for the electrophysiologic properties of antiarrhythmic drugs in general may become more apparent when other agents are studied in the same or similar models.

Modifications of Drug Effects by Ischemia

It is clear from the studies on lidocaine and propranolol that the effects of an agent on an individual cell or a small group of cells in vitro may not allow an accurate prediction of the effects of the agent on abnormal tissue and on the interplay between relatively large volumes of abnormal and normal tissues in situ. One question that should be considered initially is: Do drugs reach the ischemic or infarcted zone? Demonstration of electrophysiologic effects in ischemic and infarcted zones suggests that drugs do reach these zones, whether by direct diffusion from the left ventricular cavity where they would quickly reach Purkinje fibers located at the endocardium, or by collateral or other intact blood flow. Diffusion of drug from the normal zone to the periphery of the ischemic zone, where boundary currents arise,[8] could also occur readily. In addition, it is possible that certain drug effects are mediated indirectly through the nervous system and not by direct effects on the heart.

That both lidocaine and propranolol have different effects on ischemic and normal zones is not surprising when one considers the many ways in which ischemia or infarction may modify drug effects. Disrupted cell structure or metabolites, such as adenosine or lactate, released in the ischemic zone might modify drug effects.[9] Increased hydrogen ion concentration in the ischemic zone might enhance the local anesthetic properties of lidocaine; these properties are believed to reside in the ionic form of lidocaine which has a greater relative concentration at lower pH values.[14] The high local concentration of potassium that occurs in the ischemic zone is known to potentiate local anesthetic effects.[15] Lidocaine, for one, has recently been shown to markedly depress partially depolarized cells while having little effect on cells with normal resting potentials[16]; this property may well explain lidocaine's selective depression of conduction in the ischemic zone. If calcium-mediated slow potentials are responsible for impulse propagation in the ischemic zone,[17] certain drugs such as propranolol could have a different effect on these than on the sodium-mediated fast potentials responsible for impulse propagation in normal Purkinje fibers and ventricular muscle. Different concentrations of catecholamines may be present in the ischemic zone causing a difference of beta adrenergic blockade.

Tissue Interactions, Arrhythmias and Drug Effects

The problem of differences between drug effects in situ and in vitro becomes even more complex when one considers that many tissues interact to cause arrhythmias. In the ventricle, ischemia of the His-Purkinje system or ventricular muscle, or both, could cause arrhythmias. In the atrium, mitral valve disease causes electrophysiologic abnormalities as a result of stretch, fibrosis, ischemia or atrial hypertrophy. Atrial arrhythmias may be caused by complex interactions between normal and abnormal portions of working atrial myocardium, specialized atrial fibers and sinus and atrioventricular nodal tissue, all of which are influenced by the autonomic nervous system. Because of these complexities, it is not surprising that many clinicians find classifications of antiarrhythmic drugs based on isolated tissue studies difficult to apply to the patient.

Although the problem of extrapolating in vitro data to the in situ heart is most apparent for reentrant ar-

rhythmias, such as those that occur in acute ischemia,[12] problems also arise when examining the effects of drugs on automaticity. It may not be clear which type of tissue or group of cells is responsible for causing a given automatic arrhythmia. Further, there are different mechanisms for automatic activity, including so called "abnormal automaticity," which is characterized by overdrive enhancement rather than by overdrive suppression, an important feature of normal automaticity.[18] In addition, differences in action potential duration with associated boundary currents not only cause reentry, but also may cause diastolic depolarization with resulting automatic activity in the zone of the shorter action potential duration.[7,8] In this instance, the effect of the antiarrhythmic agent on the interplay of action potential durations would be more significant than the agent's effects on a single automatic cell in vitro.

Clinical Implications

The most important problem in basing concepts of drug actions entirely on studies of isolated tissues is the difficulty in these studies of reproducing cellular and extracellular abnormalities that occur in disease states and of evaluating the effects of the agents on the interplay and current flow that may occur between relatively large volumes of specialized and working cardiac tissues. Further, the influence of the autonomic nervous system is not directly involved in vitro, and the appropriate drug concentration for studies in vitro is unclear since it is uncertain at what local concentrations of drugs antiarrhythmic effects occur in situ.

Despite these difficulties, the recording of intracellular potentials by the microelectrode technique is still the most definitive model for understanding electrophysiologic phenomena in the heart, and efforts have been made to reproduce in vitro certain of the influences that may modify drug actions in situ. Some of these efforts include the following studies: the effect of drugs on right atrial tissue from patients with mitral valve disease[19]; the effects of diphenylhydantoin on hypoxic Purkinje fibers[20]; the effects of verapamil on slow potentials[21]; the effect of drugs on infarcted canine tissue in vitro[22]; the characteristics of abnormal automatic mechanisms[18]; and the effects of drugs on isolated tissue perfused with blood from donor animals.[23] In all of these studies, an attempt was made to reproduce one of the abnormalities, either of structure or extracellular milieu, that occur in hearts with arrhythmias. Because of the complexity of the problem and the many abnormalities that occur, such studies are still in an early phase. In the future, similar studies and those performed in the diseased heart should lead to new classifications of antiarrhythmic agents that will reflect in situ electrophysiologic properties and thus be of more use to the clinician.

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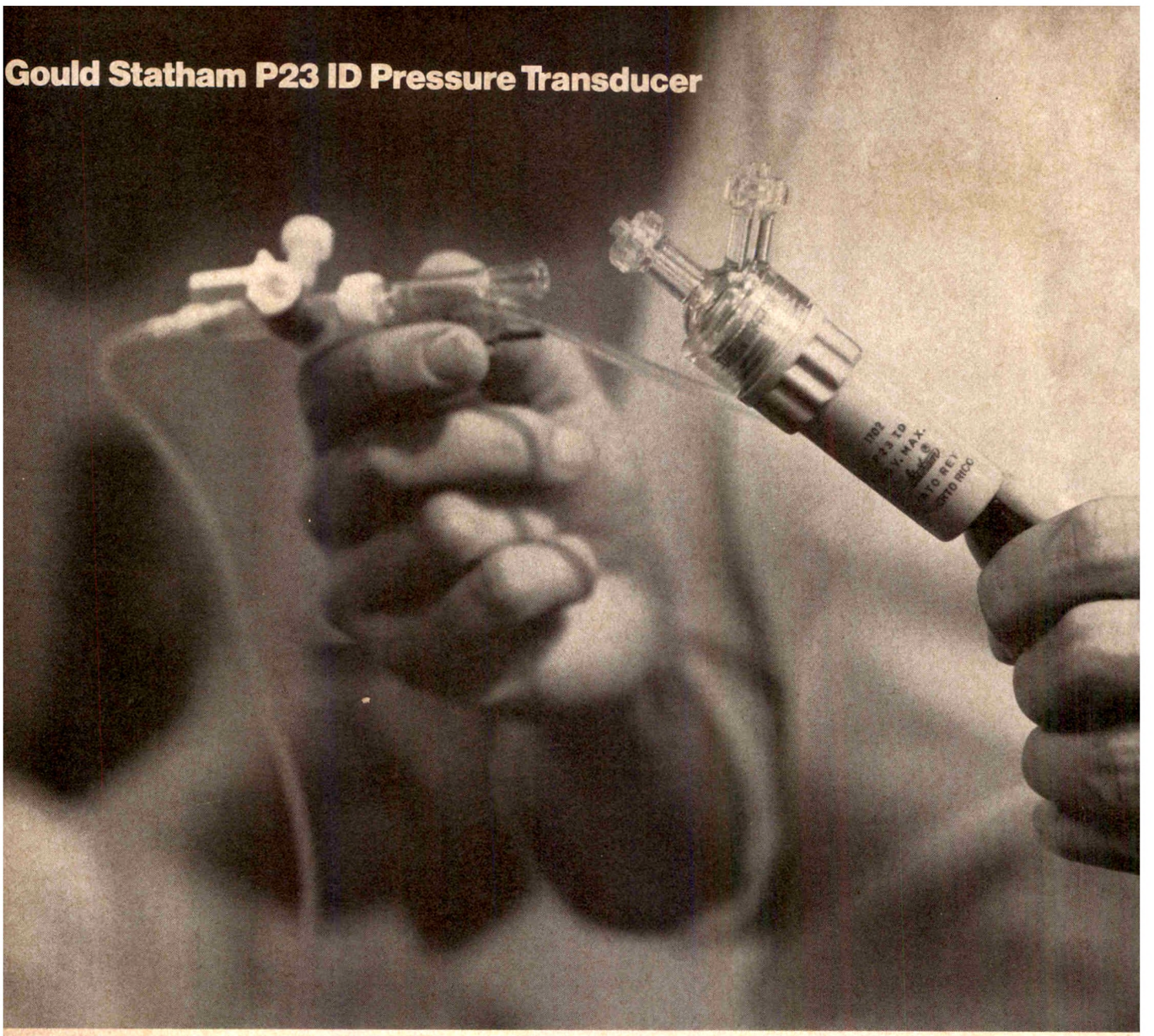

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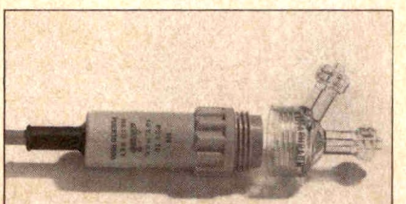

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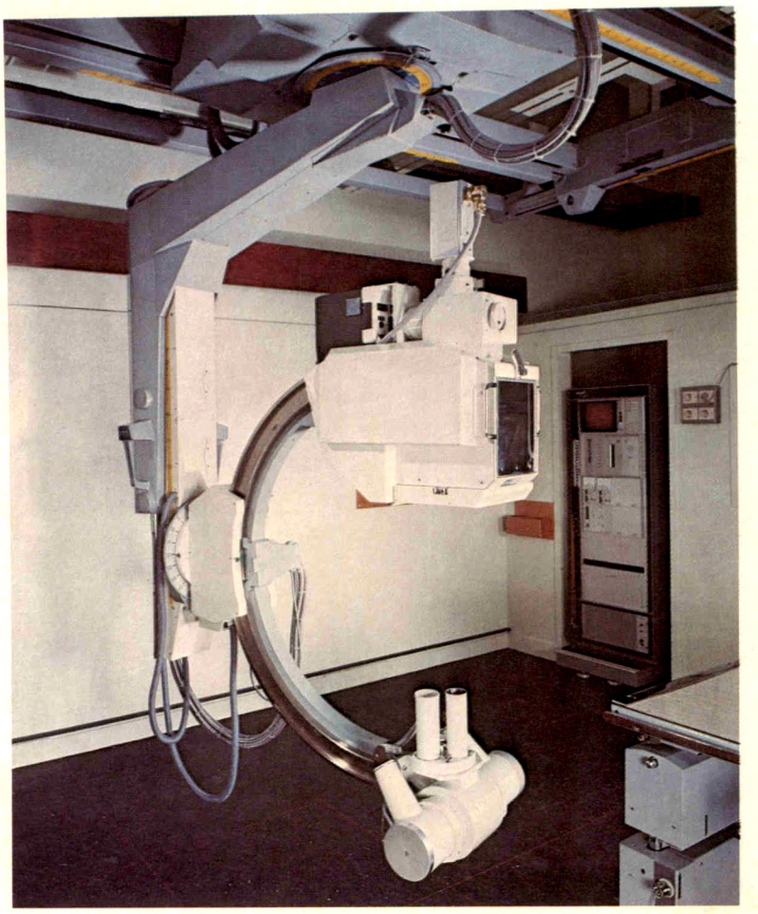

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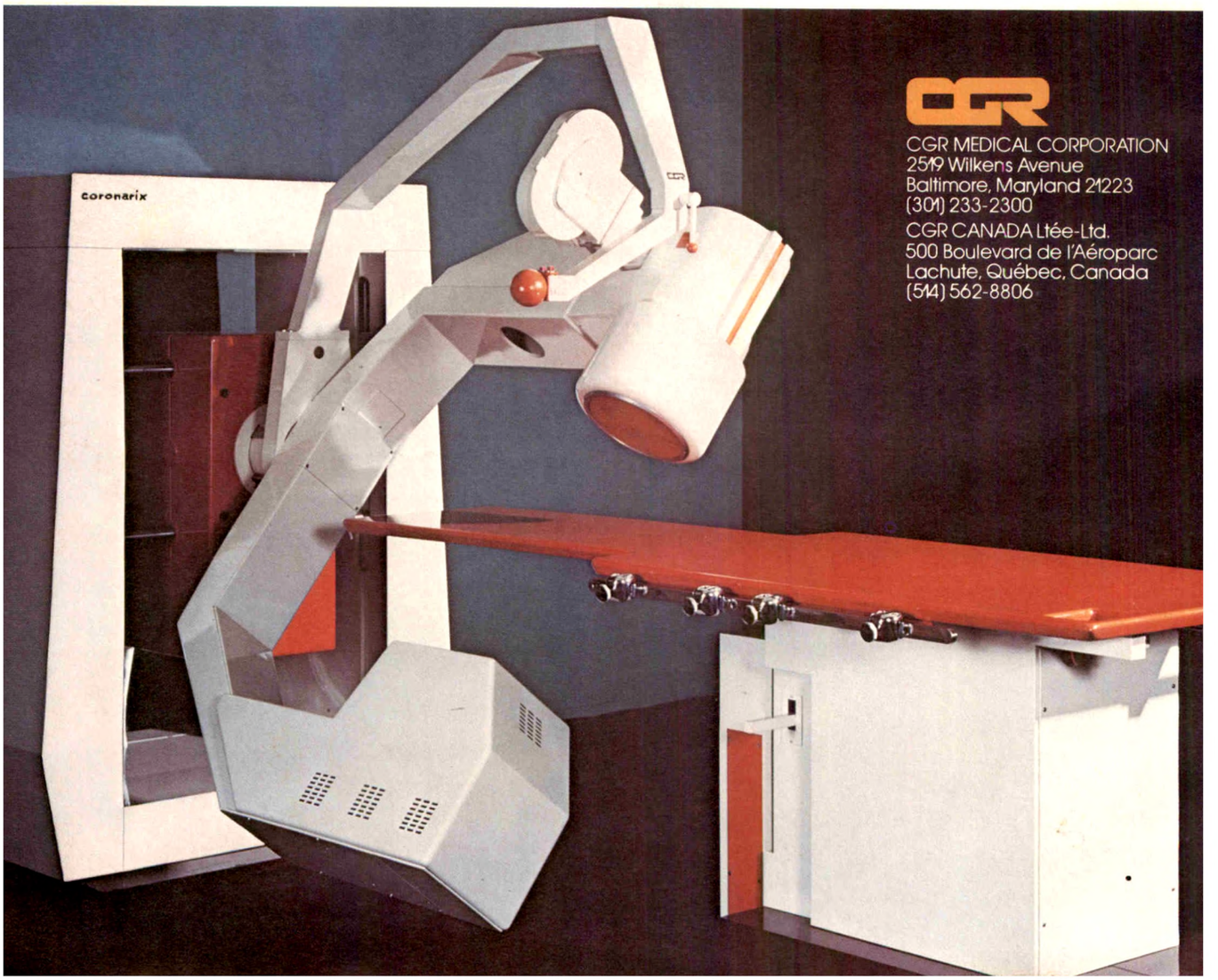

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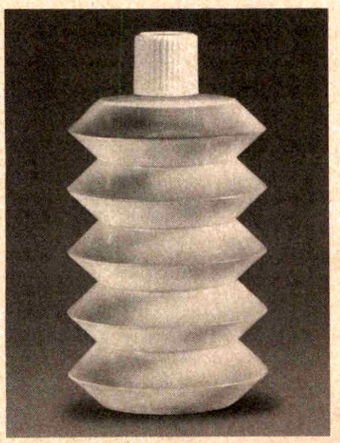

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WARNINGS Safety in pregnancy and in children has not yet been established. Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults. Hypotension may occasionally result. If severe enough to require therapy, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine. Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored, especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide. Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. Concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions). Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent. Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

PRECAUTIONS HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available. It should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively. Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response. As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental. Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection. Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

ADVERSE REACTIONS

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by unconsciousness, convulsions, paralysis, confusion or focal neurological deficit, such as numbness of the hands; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions, such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported. Papilledema, induced by plasma volume expansion secondary to the administration of diazoxide, was reported in one patient who had received eleven injections over a twenty-two day period.

Other adverse reactions: Vasodilative phenomena, such as orthostatic hypotension, sweating, flushing, and generalized or localized sensations of warmth; supraventricular tachycardia and palpitation; bradycardia; various transient neurological findings secondary to alterations in regional blood flow to the brain, such as headache (sometimes throbbing), dizziness, lightheadedness, sleepiness (also reported as lethargy, somnolence or drowsiness), euphoria or "funny feeling", ringing in the ears and momentary hearing loss, and weakness of short duration; chest discomfort or nonanginal "tightness in the chest"; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; and various respiratory and gastrointestinal findings, secondary to the relaxation of smooth muscle, such as dyspnea, cough and choking sensation; nausea and vomiting and/or abdominal discomfort, anorexia, alteration in taste, parotid swelling, salivation, dry mouth, lacrimation, ileus, constipation and diarrhea. Also, warmth or pain along the injected vein; cellulitus without sloughing and/or phlebitis at the site of extravasation; back pain; and increased nocturia. Apprehension or anxiety, malaise and blurred vision occurred on single occasions.

DRUG INTERACTIONS Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

OVERDOSAGE Overdosage may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agent suggests that the hypotension may have been caused by something other than diazoxide. Excessive hyperglycemia resulting from overdosage will respond to conventional therapy of hyperglycemia. Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

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*Marvin Moser, M.D., Assistant Professor of Clinical Medicine, Albert Einstein College of Medicine, and Chief of Cardiology, White Plains Hospital, White Plains, N.Y., in Diazoxide—an effective vasodilator in accelerated hypertension. *Am Heart J* 87(6): 791-795, June 1974.

Administration guidelines

1. Fill dry syringe with appropriate dose of HYPERSTAT I.V. Injection (20 ml ampule contains 300 mg diazoxide).

2. Hospitalized patient should be recumbent. Insert needle only into a peripheral vein.

3. Inject entire dose I.V. in 30 seconds or less. Remove needle carefully—avoid extravasation.

4. Keep patient recumbent for at least half an hour after injection; monitor BP closely until stabilized—usually 15-30 minutes.

5. If patient is to be ambulatory, measure BP in standing position before ending surveillance.

6. HYPERSTAT I.V. Injection should be continued until a regimen of oral antihypertensive medication becomes effective (generally within a few days).

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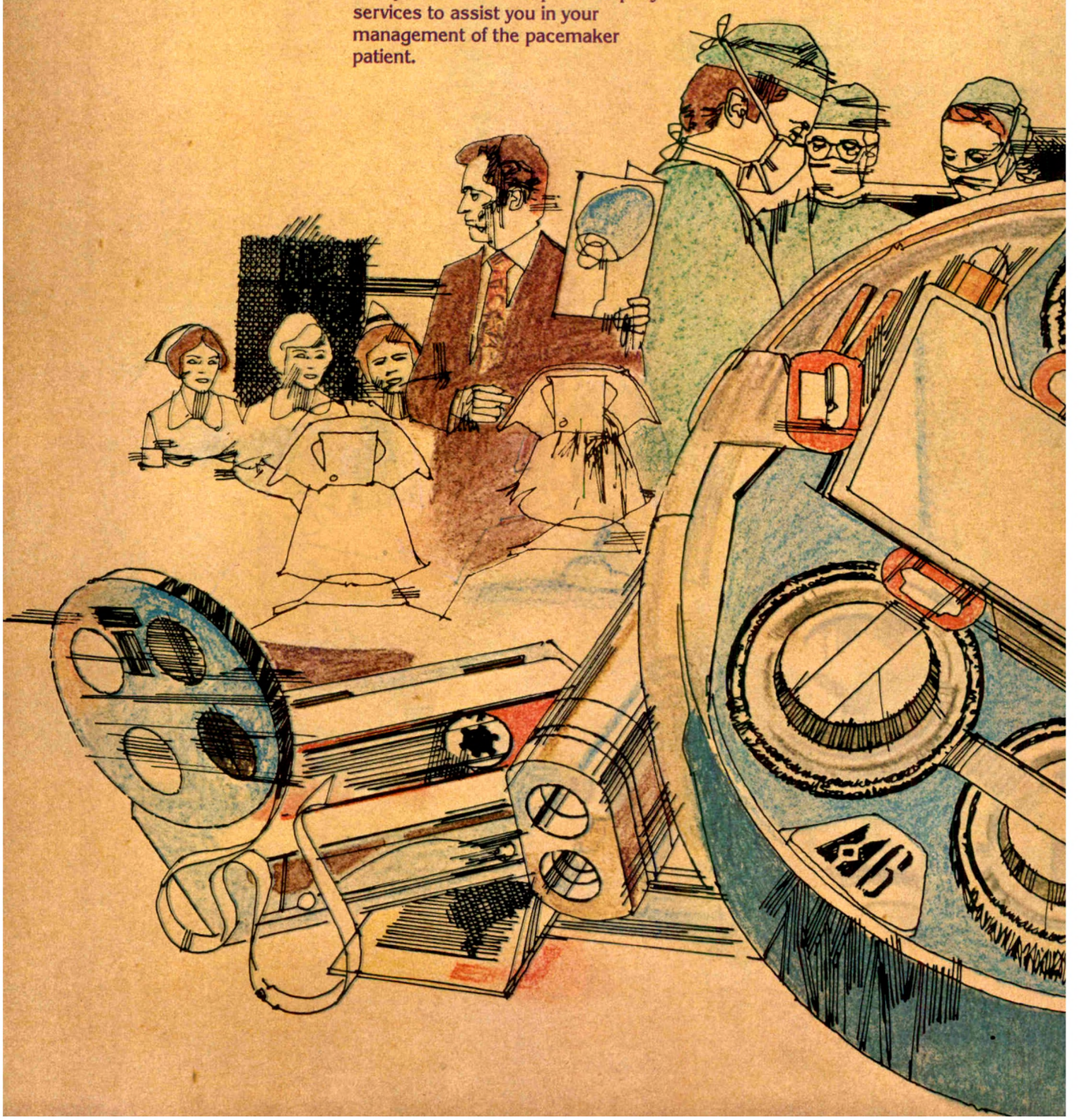

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Physiological, Pathophysiological and Diagnostical Research

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Volume 16 of the series **Advances in Cardiology** features the proceedings of the 1st International Congress on Electrocardiology (15th International Symposium on Vectorcardiography). At this meeting scientists from various disciplines, all of them sharing a common interest in the field of electrocardiology, met and discussed a number of items which should lead to a stimulation of interest in new research areas and improved clinical practice. Corresponding to the sessions of the congress, this proceedings publication is subdivided into six parts, each of which contains information of considerable importance to active participants in this growing area of study.

Clinical Application of Current Techniques and Treatment in Cardiology

6th Cardiovascular Conference in Snowmass-at-Aspen, Aspen, Colo., 1975

Vol. 17
Editor: *John H.K. Vogel* (Santa Barbara, Calif.)
X + 253 p., 51 fig., 60 tab., bound, 1976
US $ 48.50
ISBN 3–8055–2267–3

The purpose of the 6th Conference on Cardiovascular Disease, for which this book represents the proceedings, was to define the current status of treatment in the more difficult and ever-changing areas of cardiology, including acute coronary artery disease, valvular heart disease and congenital heart disease. As a valuable supplement to the individual contributions presented at the conference, this work also includes the debates which took place on the questions of when to perform valve replacement, the role of surgery in unstable angina, and whether total repair during early infancy in congenital heart disease is advisable.

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WARNING—Lasix (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Indications—Lasix (furosemide) is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.

Hypertension—Lasix (furosemide) may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix (furosemide) alone.

CONTRAINDICATIONS—Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. (See "Additional Information.")

Lasix (furosemide) is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with a history of hypersensitivity to this compound.

Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

Patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, an oral liquid preparation should be used rather than enteric-coated potassium salts.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix (furosemide).

Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

When parenteral use of Lasix (furosemide) precedes its oral use, it should be kept in mind that cases of tinnitus and reversible hearing impairment have been reported. There have also been some reports of cases in which irreversible hearing impairment occurred. Usually, ototoxicity has been reported when Lasix (furosemide) was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were often given. If the physician elects to use high dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable (for adults, it has been reported that an infusion rate not exceeding 4 mg Lasix [furosemide] per minute has been used).

Increases in blood glucose, and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix (furosemide) may lower serum calcium levels, and rare cases of tetany have been reported.

Patients receiving high doses of salicylates, in conjunction with Lasix (furosemide) may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, Lasix (furosemide) and cephaloridine should not be administered simultaneously.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue Lasix (furosemide) for one week prior to any elective surgery.

Adverse Reactions—Various forms of dermatitis, including urticaria and rare forms of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura). Rare cases of agranulocytosis which responded to treatment.

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli and acute pancreatitis.

Lasix (furosemide)-induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

Dosage and Administration

ADULTS

The usual adult dose of Lasix (furosemide) is 20 to 80 mg given as a single dose.

If the diuretic response with a single dose of 20 to 80 mg is not satisfactory, the following schedule should be used: Increase this dose by increments of 20 or 40 mg not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. The dose of Lasix (furosemide) may be carefully titrated up to 600 mg per day in those patients with severe clinical edematous states.

With doses exceeding 80 mg/day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension—The usual dose of Lasix (furosemide) is 40 mg twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50 percent as soon as Lasix (furosemide) is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix (furosemide), a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if 40 mg twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents, e.g., reserpine, rather than to increase the dose of Lasix (furosemide).

INFANTS AND CHILDREN

Pediatric Administration: The usual initial dose of oral Lasix in infants and children is 2 mg/kg body weight, given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg not sooner than 6 to 8 hours after the previous dose. Doses greater than 6 mg/kg body weight are not recommended.

For maintenance therapy in infants and children, the dose should be adjusted to the minimum effective level.

How Supplied—Lasix Tablets 40 mg (furosemide) supplied as white, round, monogrammed, scored tablets.

Lasix Tablets 20 mg (furosemide) supplied as white, oval, monogrammed tablets.

Note: Dispense in dark containers. Exposure to light may cause slight discoloration which, however, does not alter potency.

Additional Information

Toxicology

The acute toxicity of Lasix (furosemide) has been determined in mice, rats, and dogs. In all three animal species, the oral LD_{50} of Lasix (furosemide) exceeded 1000 mg/kg of body weight, while the intravenous LD_{50} ranged from 300 to 680 mg/kg. Intragastric injection of the drug in newborn rats resulted in an LD_{50} of 380 mg/kg.

The acute toxicity of high doses of Lasix (furosemide) was characterized by convulsions, paralysis, and collapse. Surviving animals often became dehydrated and depleted of electrolytes due to the diuresis induced by Lasix (furosemide). In the newborn rats, intragastric injection of the drug caused hyperactivity and anorexia.

Chronic toxicity studies with Lasix (furosemide) were done in rats and dogs. In a one-year study in rats, renal tubular degeneration occurred, with all doses higher than 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day). A six-month study in dogs revealed calcification and scarring of the renal parenchyma at all doses above 10 mg/kg (83 percent of the maximal recommended human dose of 600 mg per day).

Reproductive Studies

The effects of Lasix (furosemide) on embryonic and fetal development and on pregnant dams were studied in mice, rats, and rabbits.

Lasix (furosemide) caused unexplained maternal deaths and abortions in the rabbit when 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day) was administered between days 12 to 17 of gestation. In a previous study the lowest dose of only 25 mg/kg (2 times the maximal recommended human dose of 600 mg per day) caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality which can precede maternal deaths.

The results of the mouse study and one of the three rabbit studies also showed an increased incidence of hydronephrosis (distention of the renal pelvis and, in some cases, of the ureters) in fetuses derived from treated dams as compared to the incidence in fetuses from the control group.

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MYOCARDIAL CONTRACTILITY AND ISOVOLUMIC POWER AND RATE OF CHANGE OF POWER

Stein et al.[1] describe the clinical application of two quantities that they have recently proposed to characterize the contractile state of the myocardium: the isovolumic power and the rate of change of power.[2] These quantities contain essentially the same basic mathematical information as the power density and the rate of change of power density that we introduced in 1971[3] and formalized in 1972 and subsequent years.[4–8] Despite differences in the physics behind their equations and ours, the end results of each formulation contain the same information: the ventricular pressure and its first and second time derivatives. Therefore, both formulations should yield comparable results. The similarity in results and mathematical content is shown in Figure 1, which compares tracings in the time domain of their quantities and ours during the course of a calcium dose-transient response curve in the isolated heart preparation. The tracings were simultaneously generated by a general purpose analog computer in which the various mathematical expressions had been previously mechanized. By convention, dots over the variables denote differentiation with respect to time. Calcium was given in doses of 2 to 24 mg in increments of 2 mg. Each transient response lasted approximately 1 minute (see time scale at bottom). The tracings of power density, simply the first time derivative in our definition, are plotted immediately above the tracings of isovolumic power as defined by Stein and associates. Similarly, the tracings of rate of change of power density, simply the second time derivative in our definition, are plotted immediately above the tracings of rate of change of power according to their definition. It can be seen that, along the calcium dose-transient response curve, the behavior of corresponding quantities is essentially the same. This should not be surprising since both formulations derive from complementary approaches to the same fundamental phenomenon, that is, the change in energy in the ventricle during the phase of isovolumetric contraction. Within the unity of science each approach should be consistent with the other, either being fluid mechanics, as used by Stein et al., or nonequilibrium thermodynamics, as previously used by us. Thus, both approaches should lead to the same results. In what follows we will point out the differences in the physics behind each formulation as well as the advantages and drawbacks of each approach.

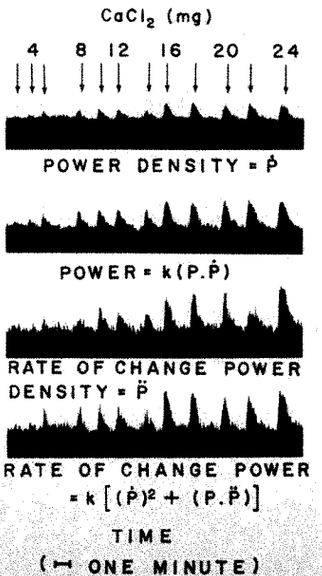

FIGURE 1. Comparison of tracings during course of calcium dose-transient response curve (see text).

The argument advanced by Stein et al. revolves about the energy spent by the ventricle in compressing the blood within its cavity during the phase of isovolumetric contraction. In our thermodynamic approach we neglected this work of compression ($\int PdV$) by considering the blood an incompressible liquid. In reality, most biologic processes take place at a practically constant volume ($dV \simeq 10^{-5}$)[9] and, even in other physical systems, the thermodynamic assumption of incompressible liquids holds good up to several hundred atmospheres of pressure.[10] Second, Stein et al. derive their quantities from considerations of actual work performed by the ventricle upon the elastic blood within its cavity. Since actual work depends not only on the capability of a system to perform but also on the conditions of its loading, there are significant problems in characterizing the state of the system by only the work it is performing. Such characterization requires a statement of the load that we show in Figure 1 as the constant (k) definitions of power and rate of change of power by Stein et al. In their definitions this constant is the quotient of the end-diastolic ventricular volume and the bulk modulus of the blood. Whereas the bulk modulus of the blood can be reasonably approximated by using that found for water, the end-diastolic volume cannot be disposed of so readily. We will return later to how this was done.

In our thermodynamic approach, the work of compression had been discarded as negligible, and the only mechanical work term left in the Gibbs equation was the displacement of a slug of blood into the aorta during the phase of ejection. Earlier, during the isovolumetric phase, there was only the development of a work potential as a result of the advance of the mechanochemical process of muscle contraction. This potential, which should not be confused with any storage of potential elastic energy, is a thermodynamic quantity representing the change in free energy in the ventricle. Physically, this quantity relates to the amount of work that the ventricle is capable of performing at each point during the rising isovolumetric phase of the ventricular pressure if the aortic valve were to open at that point. Since the valve can open only when the ventricular pressure reaches the level of aortic pressure, any such point along the curve of rising ventricular pressure reflects the work that the ventricle can perform at that particular load. Here what is truly important is to establish how readily a given ventricle can build up such potential to perform work. We[4] have shown that the rate of change of free energy, that is, the development of power density, can be identified with the first time derivative of the ventricular pressure and that, similarly, the rate of change of power density can be identified with the second time derivative. These quantities are intensive rather than extensive properties of the system and, as such, are independent of volume.

Up to this point, and irrespective of the validity of the physics underlying each formulation, both developments are afflicted by the common drawback of yielding quantities that

are specific functions of time and that can be evaluated only in terms of their peak values. Figure 1 shows that these values correspond essentially to the peak values of the first and second time derivatives of the pressure. These derivatives have long been known to medical investigators, who soon learned that their peak values, though capable of detecting changes in contractility in a given subject, varied greatly from one person to the next. As a result of the significant overlap of values, these peak quantities could not be used to define a control state for a normal population or to distinguish between states of increased and decreased contractility in different persons. Then, it must have been evident to Stein and associates, as it was to us, that more meaningful quantities than the peak values of derivatives needed to be developed.

In the article under discussion, Stein and associates divided their instantaneous rate of change of power by their instantaneous power to obtain a new quantity, their fractional rate of change of power (FRCP) which, by canceling the constants in each equation, eliminated the need for statements concerning the end-diastolic ventricular volume and the bulk modulus of the blood. The physical argument justifying this mathematical operation is that the new expression " . . . . represents the rate of change of power relative to instantaneous power developed during isovolumic contraction." We had offered a somewhat similar argument while plotting the second and first time derivatives of the pressure in Cartesian coordinates[4] (" . . . . a plot of $\ddot{p}$ vs. $\dot{p}$ represents the rate of power density generation for each level of power density gained by the system.") Although the similarity of arguments could have led to comparable results, the approach of Stein et al. yielded ambiguities in interpretation of the data that mar the formalism of their approach. Thus, their fractional rate of change of power had "no readily measurable peak value" and had to be measured at "various arbitrarily selected values of the intraventricular pressure." Ventricular pressures of 50 and 60 mm Hg "were found convenient for purposes of describing the data." "Because of the inaccuracies related to computation of the ratios of small numbers, the fractional rate of change of power was not computed during the initial portion of isovolumic contraction."

For completeness, we will show briefly how our derived quantities are free from the ambiguities afflicting their fractional rate of change of power. Graphically, our energy-averaged power density (APD) is the area under the isovolumetric portion of a plot $\dot{p}(t)$ vs. $p(t)$ in Cartesian coordinates after dividing the area by the maximal value of the isovolumetric pressure. Similarly, our power-averaged rate of generation of power density (ARPD) is the area under the curve of a plot of $\ddot{p}(t)$ vs. $\dot{p}(t)$ divided by the maximal value of $\dot{p}$. Mathematically:

$$\text{APD} = 1/p_{max} \int_0^{p_{max}} \dot{p}\, dp \text{ and } \text{ARPD} = 1/\dot{p}_{max} \int_0^{\dot{p}_{max}} \ddot{p}\, d\dot{p}$$

or their transformations:

$$\text{APD} = 1/p_{max} \int_0^{t} \dot{p}^2 d\tau \text{ and } \text{ARPD} = 1/\dot{p}_{max} \int_0^{t} \ddot{p}^2 d\tau$$

These quantities are not instantaneous values selected at arbitrary levels but unambiguous expressions representing the values of the power density and its rate of generation averaged over the entire phase of isovolumetric contraction. These average quantities should be more meaningful estimates of the events taking place during the phase of isovolumetric contraction than any instantaneous value of quantities that, by containing derivatives, are inherently more noisy and offer a lower reproducibility. For any heart cycle, energy-averaged power density (APD) and power-averaged rate of power density (ARPD) are unique numbers that, unlike fractional rate of change of power, do not require decision-making as to their point of evaluation. APD is readily obtained from photographs of the screen of an oscilloscope displaying signals of pressure and its first derivative generated by routine equipment in any cardiac catheterization laboratory. ARPD requires two differentiators in cascade. APD has a definite mathematical dependence in preload and afterload, whereas ARPD is free of this objection.

In conclusion, it seems that Stein et al. have pursued the same objectives that we had pursued earlier, that is, the evaluation of the change in energy in the ventricle during the phase of isovolumetric contraction. Either disapproving of our macroscopic thermodynamic description of this change in energy, or being unaware of it, they chose to use the more detailed description of the fluid dynamics approach. Again, within the unity of science, each approach should be consistent with the other and lead to comparable results. However, the fluid dynamics approach requires a more intimate knowledge of the details of the system as demonstrated, in this case, by the need to specify end-diastolic ventricular volume and bulk modulus of the blood. Stein and associates could circumvent the need for this knowledge only by resorting to mathematical operations that, ultimately, led to troublesome ambiguities in the interpretation of the data. Despite these difficulties, the strength of the fundamental phenomenon underlying isovolumetric contraction must have emerged through the ambiguities to allow for a reasonable separation between their patients with normal and abnormal ventricular performance. Nevertheless, we respectfully submit that the approach of Stein et al. has not improved in any way our earlier description of the change in energy in the ventricle during isovolumetric contraction nor has it yielded simpler, more accurate or more meaningful quantities to characterize the contractile state of the myocardium.

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REPLY

Our equations representative of the isovolumic rate of change of power (Moreno's Ref 2 and our Ref 1) and isovolumic fractional rate of change of power (Moreno's Ref 1 and our Ref 2) are distinct in meaning from the equations developed by Bloomfield et al. (Moreno's Ref 4). We are measuring the rate and fractional rate of change of power actually expended by the ventricle upon compression of the blood within the ven-

tricle during isovolumic contraction. They measured the rate and power-averaged rate of generation of free energy in the ventricle per unit volume of blood that potentially would be ejected. Our equations describe the actual rate of power transfer; theirs describe potential rates of power transfer. These are distinct conceptual differences. The derivations are unique because the concept is unique and original. Any notion that these expressions expand upon, modify or relate to any earlier descriptions of isovolumic energetics is fallacious.

The equations applicable to the isovolumic period which we derived and which reflect ventricular performance are:

Isovolumic rate of change of power

$$= -\frac{V_0}{M_B}\left[\left(\frac{dp}{dt}\right)^2 + p\frac{d^2p}{dt^2}\right] \quad (1)$$

$$\text{Isovolumic FRCP} = \frac{1}{p}\frac{dp}{dt} + \frac{1}{\dot{p}}\frac{d\dot{p}}{dt} \quad (2)$$

We also derived an equation representative of isovolumic power which was:

$$\text{Isovolumic power} = -\frac{V_0}{M_B}\, p\, dp/dt \quad (3)$$

Isovolumic power was affected by preload and did not separate normal patients from abnormal patients with the clarity of the isovolumic rate of change of power.[1] We did not propose that the isovolumic power be utilized as an expression indicative of performance.

All of our derivations are based upon the rate or acceleration of energy actually imparted to the blood in the form of compression of the blood within the ventricle. Equation 1 therefore indicates the rate of power actually developed by the ventricle and transferred to the blood during isovolumic contraction in the course of compressing blood within the ventricle. The values are small but real. They are derived from the only form of work actually performed during isovolumic contraction, as identified by the Gibbs equation cited by Dr. Bloomfield et al. (Moreno's Ref 4). The value of these expressions lies in the supposition that the magnitude of the acceleration of energy for the accomplishment of this work during isovolumic contraction, even though it is small, reflects ventricular performance.

The very thing that we examined, and upon which all of our work was based, was categorically excluded from all considerations in the work of Bloomfield et al. They assumed that the blood is incompressible. That is not a trivial difference in physics or in mathematical technique that permits one to obtain a common goal by parallel pathways. This is a theoretical distinction of major conceptual importance.

Moreno states that our equations contain the same information as his equations, namely ventricular pressure and their first and second derivatives. They showed that dp/dt (where p is developed pressure) could be defined as the rate of generation of free energy per unit volume of blood that would be ejected. They showed that d^2p/dt^2 could be defined as the rate of generation of power density, that is, the acceleration of generation of free energy in the ventricle per unit volume of blood that would be ejected. Whether the first or second derivatives of intraventricular pressure are defined in this fashion or defined empirically, such terms previously have been studied extensively by others. Important observations related to these expressions are quoted in our articles. However, this does not minimize the fact that these investigators showed an association of dp/dt with power and an association of d^2p/dt^2 with the rate of change of power, which was a step in the direction of defining these indexes in terms of fluid dynamics values.

Bloomfield et al. proposed that a time-averaged value of dp/dt and d^2p/dt^2 be utilized. The latter term appeared to be of potentially greater value, and they called this time-averaged value of the second derivative of pressure the power-averaged rate of generation of power density (ARPD). Although the meaning they attribute to this expression and its form of measurement differ from those of previous investigators, the end result is another exploration of a single term, d^2p/dt^2, which has been examined in detail by others.

A redefinition of dp/dt in terms of the rate of the generation of free energy in the ventricle per unit volume of blood that would be ejected and its average value, the "power-averaged rate of power-density generation," falls short of a truly meaningful expression. Since these equations fail to relate to the volume of blood that is actually ejected, these potential values do not truly describe ventricular performance. The stroke volume may vary with any given value of dp/dt or d^2p/dt^2. Therefore, the actual power or rate of change of power that the ventricle will develop may differ from the potential values described by these formulations.

Even a cursory inspection of equations 1 and 2 indicates that considerably more information is contained in each of these expressions than in computations based exclusively upon the first derivative or upon the second derivative of pressure. Both equations are a function of three important variables: pressure, dp/dt and d^2p/dt^2. In addition, equation 1 also relates to end-diastolic volume. For the first time, therefore, in a single mathematical expression that is soundly based upon theories of fluid dynamics, one is able to relate in a meaningful fashion these critical indexes of performance. Entirely new expressions result. This exceeds in value the assignment of a different meaning to a previously analyzed expression. Of a practical nature, we showed in dogs that equations 1 and 2 reflected drug-induced alterations of the contractile state and were little affected by alterations of preload or afterload. In patients we showed that equations 1 and 2 distinguished those with normal performance from those with abnormal performance.

The equation representative of the isovolumic rate of change of power (equation 1) has specific advantages: (1) Its physiologic meaning is readily apparent; (2) it is firmly based upon theories of fluid dynamics, the only assumption being that of isothermal conditions during the isovolumic period; (3) it follows the traditional concepts of hemodynamics by relating work, power and rate of change of power; (4) it is independent of assumptions related to geometry of muscle fiber orientation or synergy of contraction; (5) it relates fiber length to isovolumic pressure and its rate and acceleration in a single hemodynamic expression. Peak values were readily measured with this expression. The simultaneous measurement of ventricular volume by echocardiography and ventricular pressure during cardiac catheterization increases the practical applicability of this expression. The measurement of end-diastolic volume (V_0) is never assumed to be constant in the measurement of the isovolumic rate of change of power. (In this regard, it should have been measured after each dose of calcium chloride administered in Moreno's Figure 1. Also, the isovolumic rate of change of power showed more consistent results than the rate of power density (d^2p/dt^2). An unexplained reduction was noted with the latter after administration of 22 mg of calcium chloride.)

The isovolumic fractional rate of change of power, which is the ratio of the instantaneous rate of change of power (equation 1) divided by instantaneous power (equation 3), was also explored and appeared to be of practical and theoretical value. Major advantages of this expression are that (1) it was derived on the basis of conventional fluid dynamic concepts of work, power and rate of change of power; (2) it utilizes

variables that can readily be measured (p, dp/dt and d^2p/dt^2); (3) it yields a normalized measure; (4) its form is such that the need to measure end-diastolic volume and the modulus of volume compressibility is eliminated. The meaning of the fractional rate of change of power is clear. It represents the rate of change of power relative to instantaneous power. The expression is useful during the isovolumic period, when it refers to the energy transfer to the blood in the act of compression. It also is useful during ejection,[3] when it represents the ratio of the rate of change of useful power developed during ejection to instantaneous power. The expression is precise and unambiguous. It applies with precision throughout the entire isovolumic period. Since there is no peak value of the isovolumic fractional rate of change of power (or if there is we could not measure it) we elected to evaluate this hemodynamic variable on the basis of values at selected points during the isovolumic period. Theoretically, one could select any point during the isovolumic period in order to make such comparisons. Irrespective of the techniques of measurement and computation, ratios of the first and second derivative of pressure near the onset of the isovolumic period, when pressure is low, are subject to errors of measurement. We found this to be true utilizing digital computation techniques; it is also true if one utilizes analog techniques. As Bloomfield et al. indicate, spurious looplets were noted in their data, and integration of the area under the major true loop at times was precluded. Thus, the acquisition of precise data may not be possible at low ranges of pressure. We therefore obtained measurements only of pressures that could be determined with reasonable accuracy.

One could average the area under the fractional rate of change of power to determine an average fractional rate of change of power during the isovolumic period. Perhaps, in accordance with the style of data presentation utilized by Bloomfield et al., a presentation of the data in this form may be less arbitrary. A clear distinction among patients would be possible, and a descriptive number, with no "ambiguity," could be obtained.

In summary, our concept of measurement of ventricular performance is based upon actual work performed during isovolumic contraction. In this regard it is distinct and uniquely different from that of Bloomfield and associates and is not related to their description of the free energy that potentially could be generated during the isovolumic period. Whether their equations will prove to be more or less meaningful in terms of practical application remains to be tested. We have shown the functional value as well as the theoretical applicability of our work. Equations 1 and 2 distinguished between patients with normal and abnormal performance better than did standard isovolumic indexes. Although 3 years have passed since publication of the article by Bloomfield et al., Moreno has cited no additional references to the applicability of their equations for the evaluation of patients.

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PACEMAKER TRIGGERING (INHIBITION) BY ELECTRIC TOOTHBRUSH

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The problem of electromagnetic interference with pacemaker function has to date been more theoretic than practical.[1] Despite its known potential in older equipment,[2–4] it has not been reported to involve small hand-held home appliances except in the rare instance of electric razor incompatibility.[4–7] The following two cases are therefore of interest.

Case 1: A 73 year old woman underwent a transvenous pacemaker implantation at Montefiore Hospital and Medical Center on December 24, 1973 for treatment of third degree heart block with a normal sinus mechanism and intermittent Adams-Stokes seizures. The pulse generator, implanted in the right delto-pectoral area, was a General Electric R wave-inhibited A-2075A model. Function was entirely normal until February 18, 1975 when the patient contacted the pacemaker center to complain of having a "peculiar feeling" similar to preimplantation "feelings," while cleaning her teeth with her new electric toothbrush. Tests with the toothbrush (Squibb-Broxodent toothbrush model D11) in the pacemaker center the next day demonstrated that when it was turned on and held over or moved over the implanted pulse generator within 1 to 2 inches (2.5 to 5 cm) of the skin, it inhibited pacemaker output for sufficient periods of time for the patient's rhythm to revert to her underlying bradycardia so that she experienced the symptoms described. In the right hand, the normal position for use brought the toothbrush handle with its motor element into optimal position for prolonged inhibition (Fig. 1). With the patient's return to use of a standard toothbrush, pacemaker function returned to normal.

Case 2: An 82 year old man underwent transvenous pacemaker implantation at Montefiore Hospital and Medical Center on July 22, 1974 for treatment of right bundle branch block and left axis deviation with intermittent sinus bradycardia, intermittent third degree heart block and intermittent Adams-Stokes seizures. The pulse generator, implanted in the right delto-pectoral area, was an R wave-inhibited Medcor model 3-70A. Function was entirely normal. On February 24, 1975 this patient overheard a conversation related to toothbrush tests in the first patient and announced he had used the same toothbrush for 2 years (predating pacemaker implantation) without any ill effects. Studies in this patient, with his own and with the toothbrush used in Case 1, demonstrated similar inhibition, but an underlying sinus rhythm, at a rate just below that of the pacemaker, sustained the patient's circulation and he was entirely unaware of any physiologic

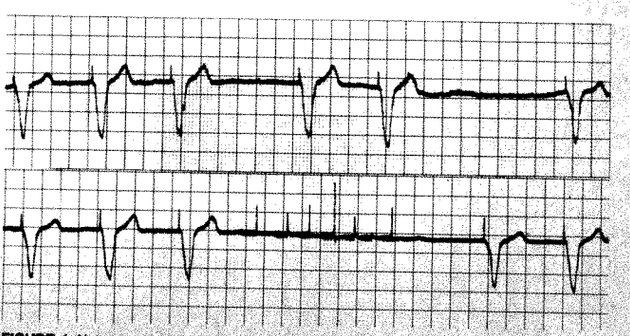

FIGURE 1. Note complete inhibition of pacemaker output with transistive toothbrush across the pacemaker. The two strips are a continuous recording. Dizziness occurred with the longer asystolic episode.

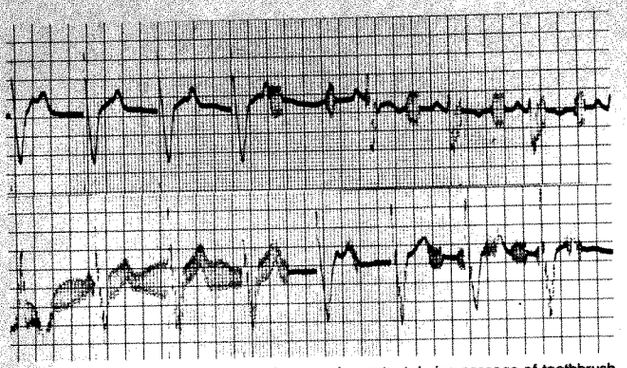

FIGURE 2. Note complete inhibition of pacemaker output during passage of toothbrush across the pacemaker. Asystole did not occur because there was an underlying sinus rhythm.

change (Fig. 2). Similar underlying sinus rhythm had been noted at each previous postimplantation examination and undoubtedly was present whenever he cleaned his teeth. As a precaution, because of his history of intermittent complete heart block, he was asked to switch to nonelectric equipment.

After these two cases, a limited sampling of the effect of this electric toothbrush on other implanted pulse generators indicated that it also could trigger, variably, Cordis models 143, 144, 145 and, in some patients, less readily, Cordis models 162 and 163 and Medtronic model 5961. It did not appear to affect Biotronik model IDP54 or IDP44 or Pacesetter model BD102. Other models of these or of other companies were not examined.

Analysis of the output of the toothbrushes revealed that they had 60 cycle alternating magnetic fields comparable with that of electric razors. At a distance of 5 cm from the brush the field was sinusoidal with a peak strength of about 1.6 gauss. At 10 cm the field strength decreased to 0.4 gauss. Unlike most small appliances, there were no significant high frequency components to the alternating magnetic field.

As in the case of electric razors, these units are more likely to cause inhibition when in motion since movement modulates the high frequency carrier wave to rates within the obligatory receptive range of the pulse generator. As opposed to electric razors, however, which in use position are 4 to 5 inches (10 to 13 cm) away from the pulse generator, the power source of the toothbrush, with its long handle, is in use position directly over the pulse generator. If any of the pulse generators went into their fail-safe "noise" mode of asynchronous pacing, which was a possibility with this interference field, it was not obvious during preliminary clinic observations, since in most of the units tested, noise rate and base pacing rate were the same.

The question of whether or not others of the new generation of handheld household electrical appliances or grooming aids can similarly trigger these or other pacemakers already is under investigation.

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PERMANENT CARDIAC PACING—I: WHO SHALL GUARD THE GUARDS?

It is an interesting but sad commentary on the human condition that, as a society becomes more coercive, it never lacks for would-be enforcers. Parsonnet[1] mandates that, for physicians who insert pacemakers, "a figure of early dislodgment higher than 5 percent calls for a review of results by a proper audit committee (now probably PSRO), and for modification of physicians' privileges." Parsonnet's rate is 4.1 percent. My rate is 2.3 percent. I therefore suggest that a figure of early dislodgment higher than 3 percent calls for a review of results by a proper audit committee (now probably PSRO), and for modification of physicians' privileges. *Quis custodiet ipsos custodes?*

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PERMANENT CARDIAC PACING—II: TRANSVENOUS VERSUS TRANSTHORACIC METHOD

Parsonnet summarily condemns the recent resurgence of interest in direct myocardial implantation—specifically the sutureless screw-in electrode for permanent ventricular pacing and concludes that the transvenous technique is the "preferred pacing method in all situations."

The thrust of Parsonnet's objections to the epicardial method for cardiac pacing are (1) transvenous pacing is associated with a "trivial incidence of complications"; (2) transthoracic pacing is neither "swift nor simple" because it cannot be performed by internists or cardiologists; and (3) transthoracic pacing by its very nature must be associated with a significant morbidity and mortality.

We believe Parsonnet's views deserve a response because he has, *ex cathedra*, dismissed unjustifiably and without documentation, the sutureless screw-in electrode—a new epicardial pacing lead that has proved to be a significant advance in the treatment of patients requiring cardiac pacing.

Parsonnet's first contention that transvenous complications are trivial is both misleading and nonreflective of the experience of other leading cardiac pacemaker centers. The two major complications of transvenous pacing (both early and late) are electrode displacement and myocardial perforation. Relative to displacement, Parsonnet reports a 4.1 percent incidence rate in 219 primary transvenous insertions applied during 1973 and 1974. However, he does not divulge electrode malpositions (dislodgment or perforation, or both) in 806 patients treated at his institution between 1964 and 1973.

Contrariwise, Brenner et al.[1] from Duke University Medical Center report a 22 percent incidence rate of transvenous electrode repositioning; Bernstein et al.[2] present an electrode displacement rate of 21.5 percent and a perforation rate of 8.7 percent; Conklin et al.[3] report a total lead complication rate of 14.5 percent; Goldstein et al.[4] had an electrode malposition

rate of 17.3 percent; Sowton et al.[5] give rates of displacement evidence of 8 percent and of exit block of 6 percent; Green et al.[6] report a 14.1 percent dislodgment rate; and Kahn[7] observed an 8 percent incidence rate of perforation.

It is readily apparent then that the true incidence of electrode malposition is not in fact trivial but disturbingly frequent. Of greater significance is that a second operation is practically always necessary to reposition the electrode, a situation that not only results in inconveniences (hospital reentry and psychologic trauma) to the patient but also predisposes to an increased risk of infection.

Other complications of the transvenous method, although less frequent, include tricuspid valve damage, major venous thrombosis, pulmonary embolism, septicemia and endocarditis, endocardial thickening and high chronic stimulation thresholds. Additionally, two recent reports[1,3] that compare the total complications of endocardial versus epicardial electrode implantations demonstrated a 2 to 3 times higher incidence rate of complications resulting from the transvenous technique.

With regard to Parsonnet's second objection, we consider his statement that neither cardiologists nor internists can perform the transthoracic procedure to be pure sophistry and irrelevant for it does not address itself to the point under consideration, which is that the ultimate role and true worth of the sutureless pacemaker technique should not be judged on the basis that only surgeons can perform this procedure.

Finally, Parsonnet indicts transthoracic pacing since it yields a greater incidence of morbidity and mortality than does transvenous pacing. We agree with this statement when the epicardial method for electrode insertion utilizes a formal thoracotomy with endotracheal intubation and general anesthesia. However, the sutureless lead was specifically designed to avoid the problems associated with a standard thoracotomy permitting lead installation by way of a limited subxiphoid or transxiphoid (extrapleural) approach using local anesthesia.

We have found the operation to be safe, easily performed and well tolerated, in a personal experience with more than 60 patients.[8] Postoperative complications were few and minimal in nature, occurring in the immediate days after surgery and consisting of pericarditis (surgical), pleuritis (left) and arrhythmic disturbances, all easily treated, self-limited and without serious consequences. There were no late complications and no patients required a second operation.

Electrode dislodgment, myocardial perforation, lead fracture or exit block did not occur in any of our patients. These observations demonstrate that the sutureless lead provides secure electrode placement permitting uninterrupted long-term cardiac pacing, the major advantage of this pacing system.

The external position of the lead to the heart is important in that it avoids the potential for development of intracardiac thromboses, valvular damage, major venous thromboses, pulmonary embolism and septicemia and endocarditis, complications which are inherent with the transvenous endocardial lead system.

Finally, we, like Parsonnet, recognize the merits of permanent endocardial pacing when the operation is performed by a trained skilled physician, but we are also convinced that the epicardial sutureless technique has special merits of its own and represents another important method for permanent cardiac pacing. This technique is our procedure of choice for almost all patients regardless of age, except for patients who are critically ill with recent myocardial infarction or with moderate or severe congestive heart failure.

We strongly believe that the sutureless epicardial lead system will assume an increasingly important role in the treatment of patients requiring permanent cardiac pacing.

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REPLY

Laforet's low incidence rate of electrode dislodgment will help me answer the arguments of Varriale and Naclerio. As for his other point, neither Laforet nor I like enforcement, but shouldn't we both accept standards for acceptable performance? And when acceptable performance is *not* obtained in Newton Lower Falls, who will bell the cat? Peer review is with us, and perhaps for good reason. The publishing of both our good and bad results, as we are doing here, is a fine way to monitor ourselves. It is certainly better than other alternatives.

Varriale and Naclerio, in disagreeing with me, have in fact supported my arguments by citing the bad experience of some pacing centers. It is unfortunate that *good* results tend to remain undisclosed, perhaps *because* they are good. A little search, however, will reveal the following incidence rates of pacemaker dislocation: 0 percent (Morse et al.[1]); 1.5 percent (Parsonnet[2]); 1.8 percent (Bette et al.[3]); 2.1 percent (Center[4]); 2.3 percent (Laforet[5]); 4.1 percent (Furman et al.[6]); 5.2 percent (Seremetis et al.[7]); and 3 percent (Siddons[8]).

Interesting data were disclosed in a national survey that I conducted in 1972 in preparation for the Groningen Pacemaker Conference. Approximately 170 pacemaker centers throughout the country responded to a questionnaire. At that time, electrode dislodgments occurred within the first week in 90 percent of the cases and later in 10 percent. Among 53 centers that reported actual data (as distinguished from estimates) the dislodgment rate of electrodes was reported as 4.8 percent (range 0 to 25 percent), and the perforation rate 1.5 percent (range 0 to 25 percent). The estimates received from another 104 centers were almost identical, with a 6 percent dislodgment and a 2 percent perforation rate. It will be interesting to see the results of a recent survey prepared for the Fifth Pacemaker Symposium held in Tokyo in March 1976.

As for the insinuation that I had neglected to report my previous experience with 806 patients, please note my previous report[2] of a 1.5 percent dislodgment rate. For the purposes of my editorial I had merely reviewed our most recent experience. Apparently we had become a little slipshod of late.

(Please note that our 4.1 percent figure of dislocations *includes* perforation, malposition and dislodgment.)

Varriale and Naclerio call attention to the other complications of transvenous pacing as if there were no significant problems with transthoracic pacing. Each technique has its own specific set of problems, but of the frightening transvenous list that they reported, we have seen *no* case of tricuspid damage, major venous thrombosis or pulmonary embolization in almost 1,400 transvenous implants. "Catheter fever" is extremely rare, occurring only twice in our experience. And, to be fair, we must remember that many complications in the list occur with *either* system. High threshold occurs with *any* electrode; the route of insertion is irrelevant. But when infection occurs around a pulse generator that requires its removal, how will Varriale and Naclerio get the transthoracic electrode out? It will require a thoracotomy for removal of infected transthoracic electrodes. Here is a significant and important distinction between the two operative methods.

As for the differences in mortality and morbidity in transthoracic and transvenous pacing, there is ample evidence in almost everyone's experience to support the relatively benign nature of transvenous pacing, despite its unique difficulties. In the series of Varriale and Naclerio of 60 patients with myocardial wires, were there no operative deaths? And why do they minimize complications that they have seen?

I don't believe that transthoracic pacing is *never* indicated. At present it appears to be at best an alternative, but less safe, approach, to be used only in special circumstances.

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MEDICOLEGAL IMPLICATIONS OF PACEMAKERS

Dreifus and Cohen[1] list a variety of possible problems of implanted pacemakers, suggesting that the physician may be legally liable for most, if not all, of them. This does not make sense legally or medically. As written, their editorial presents a variety of options for the unscrupulous lawyer and the litigious patient.

I also take exception to some of their suggestions. I do not know of anyone who implants redundant pacemaker systems to protect against lack of pacing. Even if this were a practice, it is certainly not conventional or customary. I am also puzzled by the term "minor wire fracture." Either a wire is broken or it is not.

I do not know of any appropriate electrophysiologic studies that will guarantee that atrioventricular conduction will not return in a patient who has had heart block or that retrograde conduction will not occur as a result of ventricular pacing.

I also take exception to the statement that patients should be warned about probable malfunction in the presence of microwave ovens, radar, radio broadcasting stations, magnetometers, and the like. Malfunction of pacemakers in the presence of these sources of electromagnetic interference is improbable.[2,3]

The authors are correct in saying that "negligence, as such, may not be the principal legal hazard in the field of cardiac pacemakers." I do not believe that it is. They also state that the clinician is faced with new challenges. I suggest that one of these is the malpractice insurance problem. Let us not contribute to it unnecessarily.

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REPLY

Our editorial did not suggest that redundant pacemakers should be implanted. It only pointed out that this was done on occasion when the patient demanded such a system knowing he was totally pacemaker-dependent, or the circumstances were such that the risk of a double implantation was much less than the possibility of wire dislodgment, loss of pacing threshold or failure of an older system compromising the life of the patient.

The term "minor wire fracture" is taken out of context. This wording was used so as to emphasize the possibility of minor fractures not being detected by ordinary methods of pacemaker testing or X-ray examination. These wire fractures are often subtle. They are transient phenomena and are difficult to detect in many instances. Only when the wires entirely separate and do not enjoy connection by a "saline bridge" does wire fracture become quite apparent. Hence, the statement that "a wire is either broken or it is not" is not always true, and I'm sure Smyth is aware that a saline bridge between the two broken ends of the wire can cause pacing at some times and not at others. Possible pacemaker malfunction in the presence of microwave ovens, radio broadcasting stations, and the like is common knowledge among patients, and it should be the duty of the physician to make it clear that these are possible hazards although not very probable.

Finally, the recitation of the possible problems of legal liability in tort related to charges of malpractice against consulting or treating physicians, surgeons, hospitals and manufacturers is with us now. The stimulus for this editorial emerged from the communication by Segall[1] on legal aspects of cardiac pacemakers. One cannot sweep malpractice "under the rug" and hope that it will just go away. When physicians are made aware of their responsibilities and of the ways in which we can cope with the problems that are bound to occur because of the very nature of the complications and hazards of implanted devices, we will reach some reasonable control over this unfortunate situation.

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MEDICAL VERSUS SURGICAL THERAPY IN LEFT ANTERIOR DESCENDING CORONARY ARTERY DISEASE—I

In important respects, the patients in the medical and surgical groups of Kouchoukos et al.[1] are not comparable. Of the 24 medically managed patients, only 7 (29 percent) had a truly proximal stenosis, whereas in 17 (59 percent) of the 29 surgically treated patients the lesion was proximal to the first septal or principal diagonal artery. Twice as many of the medically managed patients (10 versus 5) were at low risk as a result of prior occlusion of the left anterior descending coronary artery.

In this, as in any retrospective nonrandomized study, questions of patient selection are crucial. Why were some patients operated on and others not? A recanalized occlusion or a gradually tapered 75 percent lesion in a small anterior descending artery is much less likely to lead to surgery than is a 90 to 95 percent irregular or ulcerated stenosis in a large system. Evidence of close similarity of lesions in the two groups of patients is not presented. I do not see how the authors can conclude that "operation should not be used to prevent myocardial infarction or death from myocardial disease even in patients with high grade stenosis of this [left anterior descending] artery."

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REPLY

There are no data in our study or in the natural history studies we cited to suggest that among patients with stable angina there are appreciable differences between the behavior of those with a high grade proximal stenosis and that of patients with complete occlusion.

The reasons that some patients were operated on and others were not were given as clearly as possible in the text. We are not aware of published data supporting the concept that patients with a recanalized occlusion or a gradually tapered 75 percent lesion in a small anterior descending artery are at less risk and therefore less likely to undergo operation than those with a 90 to 95 percent irregular or ulcerated stenosis in a large system. Such a difference may exist and may be important, but this would create subsets of patients within the subset of those with anterior descending coronary disease and stable angina, and, to our knowledge, sufficient numbers of patients within these subgroups treated medically and surgically are not available for statistical comparison. The extent of collateral circulation to the distal vascular bed is probably as (or more) important in determining the probability of myocardial infarction and death as is the severity or site of stenosis.[1] The patients in our series, by definition, had adequate collateral circulation to the distal vessel.

Our patients had *stable* angina, and the conclusions can only be applied to patients in this category with the observed angiographic and hemodynamic findings. Additional studies in patients with unstable angina or with anatomic variants may lead to different conclusions. But until such information becomes available, and until the results of ongoing randomized studies of medical and surgical treatment of coronary artery disease are known, our data and the data on the natural history of left anterior descending coronary disease referenced in our article appear to support our conclusions.

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Reference

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MEDICAL VERSUS SURGICAL TREATMENT IN LEFT ANTERIOR DESCENDING CORONARY ARTERY DISEASE—II

Kouchoukos et al. found "no statistically significant differences between the usual levels of activity required to produce angina or dyspnea on exertion" in their medically and surgically treated patients. However, objectively determined exercise tolerance time was 50 percent higher in their medically treated patients (6 versus 4 minutes, $p < 0.01$). Moreover, angina pectoris was objectively found to be the limiting factor during treadmill testing in only 52 percent of these medically treated patients with stable angina pectoris. These data raise the possibility that, in spite of apparently comparable anatomic disease, myocardial perfusion through collateral vessels or otherwise may have been better in the medical group. It is striking that the incidence rate of critical stenosis proximal to the first diagonal branch was 59 percent in the surgically treated group but only 29 percent in the medically treated group, and that disease in other vessels, although considered insignificant by the authors, was present in 35 percent of the surgically treated and in only 12 percent of the medically treated group. Is it possible that in some of these patients the decision to institute medical treatment was based on an exercise tolerance time of 6 minutes or better on treadmill, lack of anginal provocation during treadmill testing, absence of critical stenosis proximal to the first diagonal or absence of disease in other arteries? If these factors played a role in decision-making, the medically treated group would indeed be expected to have a better prognosis and the comparison may not be entirely valid.

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REPLY

Although there was a statistically significant difference in the treadmill exercise tolerance time in the medically and surgically treated groups, angina was the limiting factor during treadmill testing in 52 percent of the former and in 65 percent of the latter, and this difference was not significant. One possible interpretation of these data is that myocardial perfusion through collateral vessels or otherwise may have been better in the medical group.

The incidence rate of critical stenosis proximal to the first diagonal branch also differed in the two groups, but seven medically treated patients with such lesions neither died nor sustained a myocardial infarction in a mean follow-up period of 36 months. The natural history studies we cited confirm that mortality is not significantly greater in such patients than

in patients with more distal disease. There was a further difference between groups in the incidence rate of stenosis in other vessels, but none of these stenoses were greater than 50 percent, and thus were not considered suitable for bypass grafting. It is possible that the long-term effects of these lesions could account for some of the observed differences in the two groups. However, additional follow-up has documented progression of disease in other vessels in both therapeutic groups.

The specific reasons for deciding on medical or surgical therapy were not critically analyzed. In some patients treated medically, the decision not to advise operation could have been based on adequate exercise tolerance, lack of anginal provocation during treadmill testing, absence of critical stenoses proximal to the first diagonal branch and absence of disease in other arteries. However, patients with similar findings also had bypass grafting. Furthermore, other patients in the medically treated group did not fulfill these criteria, and their subsequent course has been documented. Despite the inclusion of the latter patients, the prognosis for left anterior descending coronary disease was found to be good and is supported by the natural history studies quoted.

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HEART VOLUME AND ISCHEMIC HEART DISEASE: EPIDEMIOLOGIC CONSIDERATIONS

Tibblin et al.,[1] describing the relationship of heart volume to ischemic heart disease, stated that "mean values for heart volume did not differ significantly ($F = 1.25$; d.f. = 3), but volume tended to be greater in the two groups with ischemic heart disease ['nonfatal myocardial infarction' and 'fatal ischemic heart disease' versus 'other deaths' and 'no disease']."

Such a tendency might more easily reach biologic or statistical significance if the following points are kept in mind:

1. The patients with disease and control subjects (retrospective investigation) were identical in age (50 years old) when heart volume was measured. Pre-myocardial infarction ischemic heart disease does result in larger heart volume.[2,3] However, this is less likely to be observed in an older population because age itself is directly related to heart volume[3,4]; that is, older persons have a larger heart. A 50 year old would have a large heart regardless of the presence or absence of disease. The chances of noting volume differences between cases and control subjects would thus be reduced.

2. When observing heart volume, one should likewise examine the influence of blood pressure on the myocardium. A positive association has been demonstrated between blood pressure and heart volume.[5] Furthermore, in the earlier stages of exposure of the heart to elevated pressure, a sizable proportion of hearts react with concentric, lumen-encroaching, hypertrophy of the left ventricular myocardium.[3,6] As a result, the increased blood pressure can produce hearts both smaller and larger than normal. The former tend to reduce the average heart volume of patients with disease and, in turn, lead to a value more similar to that of the control population.

3. It might prove worthwhile to examine the time of occurrence of the ischemic heart disease during the 10 year follow-up period. The patient with a larger diseased heart runs a more severe and rapid course than does the one with a smaller diseased heart.[7] It is possible that the extent of the difference in volume is, in addition, a function of the point in time of follow-up and that the differences might become diluted the longer the duration of follow-up. In other words, "larger" hearts die sooner.

4. Are the patients with ischemic heart disease (and, thus, their heart volume measures), stemming from the sample drawn in 1963, representative of all persons with such disease found in the total population of Göteborg during the same 10 year follow-up period? The question of comparability of patients and control subjects (the latter, for the most part, a larger, randomly chosen normal group) arises.

We believe that heart volume differences are underestimated when such items are not considered.

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REPLY

Clinical ischemic heart disease is often associated with increased heart volume. Thus, patients who have survived a myocardial infarction generally have a bigger heart, as determined radiographically, than normal but heart size within normal limits was found in about 30 percent of nonselected patients aged 27 to 67 years with a first infarction.[1] Increased heart volume is a risk factor for death *after* a first infarction.[2,3]

In patients with angina pectoris the heart size measured by roentgenogram may be normal or increased. Thus, in the 18 men aged 50 years who had angina pectoris according to a questionnaire in 1963 the heart volume was 435 ± 79 ml/m^2 body surface area as compared with 392 ± 60 ml/m^2 in the rest of the sample (no. = 829). These findings can be explained by well known pathophysiologic mechanisms.

Our study was a prospective study of a general population sample of men aged 50 years, and 88 percent of the sample participated. Thus, it was *not* a case-control study, and there can be no serious question as to its representativeness considering this high participation rate. We do not agree that the prospective study was started in too old a population; only four of the men randomly selected for this study had died of ischemic heart disease between the ages of 37 and 50 years. Thus our subjects were young enough to enable study of most persons who were going to have clinical ischemic heart disease.

One important aim of the study was to find factors that would predict clinical ischemic heart disease. In addition to those factors mentioned in our paper, we have studied others including various data from a maximal exercise test.[4,5] Using all available information we still find that several men will suffer a myocardial infarction with very few premorbid indications.

In a multivariate analysis in which blood pressure, serum

cholesterol, smoking habits and some other variables were studied simultaneously according to previously reported methods,[6] increased heart volume was not associated with the development of myocardial infarction. It should be emphasized that our analysis of heart size as a risk factor is based on roentgenologic determination of heart volume with a technique used more often in Sweden than in other countries. Our results thus cannot be compared with those of the Framingham-Albany study in which electrocardiographic signs of left ventricular hypertrophy were analyzed.

The finding that there was a trend toward a larger heart in those men later developing clinical ischemic heart disease might indicate that the state of the myocardium is of importance for the clinical course. However, not only increased blood pressure but also heavy physical exertion tend to increase the size of the heart, making interpretation of the finding of a slightly larger heart difficult.

We also analyzed heart volume in relation to myocardial infarction with shorter follow-up, but this was of no greater predictive value.

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6. **Wilhelmsen L, Wedel H, Tibblin G:** Multivariate analysis of risk factors for coronary heart disease. Circulation 48:950–958, 1973

COMMENT

The reply by Tibblin et al. leaves much unanswered. First, their study is a case-control (or retrospective) analysis. Although the original design in 1963 utilized prospective methods, the data now being compared were acquired in the past.

Our point regarding the possible lack of a representative group of cases stems from the application of these two approaches. By eliminating patients with myocardial infarction (no. = 12) at the beginning of the study (a necessary condition for cohort investigations of myocardial infarction) patients with infarction (but not control subjects) are inadvertently selected out from the retrospective analysis. Furthermore, 118 persons from the original cohort refused to participate. These appear to be sicker persons (on the basis of data on sickness benefits) who might have been more likely to suffer from ischemic heart disease and, in addition, tending to have a larger heart. As a result, these "high risk" persons are also omitted from the analysis. Whereas now only 50 are classified as cases, the possibility remains that a difference in heart volume might occur with the addition of the 12 cases cited plus other cases stemming from nonresponse.

It was mentioned that "In a multivariate analysis in which blood pressure, serum cholesterol, smoking habits and some other variables were studied simultaneously according to previously reported methods increased heart volume was not associated with the development of myocardial infarction." What precisely is the source and basis for this statement? In addition, were similar multivariate results also found regarding other conditions of ischemic heart disease (that is, angina and electrocardiographic findings)?

The population studied in the original sample was of age 50. It is difficult to view them otherwise, and thus our original comment appears to hold.

Lastly, we are uncertain about the effect of follow-up on heart volume differences in the groups studied.

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DIAGNOSIS OF LEFT ANTERIOR HEMIBLOCK

Yano et al.[1] use left axis deviation of −45° or greater as their basic criterion for left anterior hemiblock. Cases with an axis of −30° to −44° they call left axis deviation. Yet both situations constitute left axis deviation, regardless of whether one is more important or more marked than the other. A most important error is their diagnosis of left anterior hemiblock using the sole criterion of axis deviation so that a single degree of axis can alter the diagnosis. Rosenbaum et al.[2] originally wrote in regard to left anterior hemiblock that the decision to set the inferior AQRS limit at −45° was an *arbitrary* choice.

Yano et al. ignore the electrocardiographic criteria suggested by Medrano et al.[3] These include a delay in the time of inscription of the intrinsicoid deflection in lead aVL, usually greater than 0.045 second. We[4] have recently correlated the axis criteria with signs of intraventricular conduction delay and concluded that left axis deviation can not be considered synonymous with left anterior hemiblock and that in some cases with minor degrees of left axis deviation left anterior hemiblock may be present. Furthermore, when associated with an inferior infarction, left anterior hemiblock is extremely difficult to diagnose with a single electrocardiogram.[5,6] It is impossible to accept the diagnosis of left anterior hemiblock in this situation merely because the QRS axis is −45° and not −44°. If the tracings of Yano et al. are amplified and the intrinsicoid deflection in lead aVL is measured it will be noticed that in their Figure 2 with a QRS axis of −30° the intrinsicoid deflection is normal; in Figure 3 with left axis deviation at −60°, it is frankly delayed (0.055 second), meeting both criteria for hemiblock. But in Figure 4, labeled left anterior hemiblock with inferior myocardial infarction, the intrinsicoid deflection in lead aVL is normal. Thus, hemiblock is probably not present.

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REPLY

Admittedly, there are no well established, definitive criteria for left anterior hemiblock. The main purpose of our study was not to defend a particular definition, but to see whether the clinical and epidemiologic evidence would, in general, support the separation of persons with left axis deviation into moderate and extreme (left anterior hemiblock) groups. An arbitrary value of −45° was employed as the dividing line simply because it has been the most commonly used criterion for left anterior hemiblock since Rosenbaum's postulation.

In many other electrocardiographic abnormalities, arbitrary values for intervals, duration or amplitudes are used as diagnostic criteria. Misclassification of borderline cases is a problem with all such criteria, but such values are still broadly useful. Categorization according to delay in onset of the intrinsicoid deflection, as suggested by Horwitz, also depends on an arbitrary criterion. Why 45 and not 44 msec? Such delay may well turn out to be a useful criterion for left anterior hemiblock, but it now rests on extrapolation of experimental data from the dog heart. Its general acceptance as a necessary criterion for left anterior hemiblock in man would require further verification by histopathologic studies.

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A MISPLACED PEARL?

In the article by Tempo et al.,[1] I came across the statement, ". . . . women with mild mitral regurgitation having been said to be 'short, thin and flat-chested'," citing Reference 16. I referred to Reference 16 and found it to be Gastroenterology by H. L. Bockus. Although Bockus's textbook is a classic, I found it hard to believe that he would be describing the muscular-skeletal appearance of ladies with mitral regurgitation. In fact, pages 238 and 241 of his textbook do discuss what Bockus knows best—gastroenterology and, in particular, hiatus hernia. I would still appreciate the reference to this classic pearl that women with mild mitral regurgitation are "short, thin and flat-chested."

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Reference

1. **Bon Tempo CP, Ronan JA Jr, de Leon AC Jr, et al:** Radiographic appearance of the thorax in systolic click-late systolic murmur syndrome. Am J Cardiol 36:27–31, 1976

REPLY

The quoted pearl, inadvertently attributed to Reference 16, should have been attributed to Reference 17 (Leighton RF, Page WL, Goodwin RS, et al: Mild mitral regurgitation. Its characterization by intracardiac phonocardiography and pharmacologic responses. Am J Med 41:168–182, 1966). In our article, the first mention of Reference 16 correctly refers to Bockus's book; it is the second mention that is incorrect.

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VARIANT ANGINA—I

Not all angina with S-T segment elevation occurring at rest is the "variant angina pectoris" of Prinzmetal. As a consequence, Shubrooks et al.,[1] in purporting to describe the clinical and anatomic spectrum of variant angina, and the results of coronary bypass surgery for it, may have instead presented a mixed group of patients, not all of whom necessarily had variant angina.

It is not rare to encounter in the coronary care unit a patient whose exertional angina has abruptly increased with the development of repeated episodes of angina at rest associated with S-T segment elevation. Most of these patients have severe stenosis (greater than 90 percent of the diameter obstructed) of at least one major coronary artery and could be loosely included in a category of "preinfarction" angina since many will subsequently have a myocardial infarction. The extreme severity of the stenosis seen in the arteriogram is probably sufficient to explain the intermittent insufficiency of a totally fixed coronary blood flow in the face of the modest increases in myocardial oxygen demand that occur episodically even at rest. Although it is possible that coronary spasm plays a role in the attacks, one does not need to evoke such a mechanism to explain events in these patients who in our experience also obtain excellent results from coronary bypass surgery. As many as 7 of the 20 patients presented by Shubrooks et al. (particularly those whose angina started out as exertional angina) may have belonged in this category rather than in that of variant angina. The cessation of attacks in 8 of 10 patients during intraaortic balloon pumping is consistent with this possibility; that form of treatment is not established as likely to prevent episodic coronary spasm (presumably the mechanism for attacks of variant angina), whereas there is good evidence that it is effective in relieving myocardial ischemia due to severe fixed coronary obstructive disease.

One wishes that the authors had described the degree of coronary obstruction more specifically than merely "greater than 70 percent fixed obstruction." There is evidence to indicate that obstructions of greater than 85 percent of the luminal diameter of a coronary artery are usually required before a decrease in resting coronary blood flow occurs.[2] Coronary obstruction of greater than 70 percent but less than 85 percent in the patients having neither symptoms of angina nor electrocardiographic signs of ischemia with stress testing are not rare. Therefore, patients with stenosis in this range who have angina at rest with S-T segment elevation unassociated with marked changes in blood pressure or heart rate are likely to have an unusual pathophysiologic basis for their attacks, and many patients with variant angina present this way. One cannot tell how many of the patients of Shubrooks et al. fit into this category of patients who, in my experience and that of others,[3,4] are less likely to be cured of rest angina by coronary bypass surgery than suggested by the report of Shubrooks et al.

Patients such as those described by Shubrooks et al. are often difficult to categorize as having either variant or "preinfarction" angina especially when they are first admitted to a coronary care unit. There are therapeutic and prognostic reasons for attempting such a differentiation, however. When the patient is having angina at rest with S-T segment elevation in the face of coronary stenoses that are inappropriately mild for such symptoms, before deciding to perform surgical therapy one should attempt to prove that the fixed stenoses in question are crucial to the production of the patient's attacks by trying to provoke an attack with atrial pacing or carefully monitored exercise testing. The failure to cause an attack with moderate to severe cardiac stress suggests an

unusual pathophysiologic feature, such as coronary spasm, which may not be relieved by coronary bypass grafting.

Shubrooks et al. are to be congratulated for the excellent symptomatic results they report in their surgically treated patients, but since symptoms can sometimes be relieved by coronary surgery even when the grafts are occluded, reports of this kind should also include the results of postoperative electrocardiographic stress testing. It is interesting that the only two patients in this series with high grade coronary stenosis who were treated medically also obtained excellent symptomatic results.

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VARIANT ANGINA—II

Shubrooks, et al. state that all but one of their patients "had progressive, unstable angina for 1 hour to 1 month, leading to hospitalization for increasing frequency and duration of severe pain" and that 12 of their patients "had angina on exertion as well as during rest; in 7, the pain began with exertion only and progressed to pain during rest."

This description does not fulfill the criteria for variant angina pectoris; these patients fit the category of unstable or progressive angina pectoris; probably the only cases of this group with genuine Prinzmetal's angina are patients 18, 19 and 20. These patients had pain *only* during rest, had normal coronary arteries as shown by angiography and were not subjected to surgical treatment.

The outstanding differences regarding clinical progress, angiographic findings and surgical results between their group of patients and those of other series, confirm that their group cannot be categorized as having variant angina.

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Reference

1. **Prinzmetal M, Kennamer R, Merliss R, et al:** Angina pectoris. I. A variant form of angina pectoris. Preliminary report. Am J Med 27:375–388, 1959

REPLY

The original description of variant angina by Prinzmetal et al.[1] was a clinical description only. Although "hypertonus" of a coronary artery was suggested as a possible etiologic mechanism, one of their original two patients did indeed have a positive exercise test, thereby indicating that a fixed coronary lesion was possibly present. Prinzmetal et al. thought that a lesion in the "large" coronary arteries was responsible for variant angina pectoris. Thus, a major point of our paper is that the *clinical* presentation of variant angina can be associated with a variable anatomic spectrum and that the anatomic presence or absence of fixed coronary lesions is the important factor in selecting patients for coronary bypass surgery.

We believe that the term "preinfarction angina" should be avoided since it obviously is a retrospective diagnosis. We subscribe to the term "unstable angina pectoris" as used in most centers. All of our patients presented with unstable angina, and the electrocardiographic phenomenon of elevated S-T segments with pain and subsequent return to baseline after pain did not differentiate between patients with high grade fixed stenotic lesions and those with minimal or no disease (some of whom can be shown to have spasm). The only clinical clue was the additional presence of exertional angina or a positive exercise test in those patients with fixed stenosis, whereas the three patients (and four more subsequently) with "normal coronary arteries" had pain at rest only. Nevertheless, the physician whose patient has unstable angina at rest and S-T segment elevation does not have the hindsight advantage of knowing the subsequent outcome. Thus, it would seem less important to differentiate "variant" from "preinfarction" angina than to identify patients with and without severe fixed coronary lesions, for therein lies the basis for the important therapeutic decisions. The published studies to date agree that patients with variant angina but with angiographically invisible or insignificant coronary artery disease are not benefited by surgery, probably because of rather diffuse spasm. Indeed, MacAlpin et al. (his Ref 3) attest to the difficulties in operating on patients with "spasm." However, they also suggest that even patients with severe fixed lesions will do poorly after coronary bypass surgery. Our experience indicates that this is not the case. In fact, the excellent clinical results in those patients with fixed lesions who had coronary bypass surgery suggest that we cannot "presume the mechanism for attacks of variant angina."

All of our patients with obstructive lesions had at least one lesion resulting in 85 percent or more luminal narrowing. The designation of greater than 70 percent obstruction was used only to indicate stenosis generally considered to be hemodynamically significant. We agree that patients with lesser degrees of stenosis associated with pain at rest, rather than on exertion, without marked changes in blood pressure or heart rate may be more likely to have spasm as a precipitating factor of ischemia and would thus be less likely to benefit from surgery. However, even with lesions of greater than 85 percent narrowing, which are probably associated with decreases in resting coronary flow, the cause of episodic ischemic attacks is unclear although, as suggested, these attacks could be related to small increases in myocardial oxygen demand occurring episodically at rest.

Too few of our patients were treated medically to permit comparison of results of medical and surgical therapy. We wished to indicate that surgery *can* be successfully accomplished with good results for the majority of those patients presenting with Prinzmetal's angina who have severe fixed obstructive lesions and that angiography is essential in identifying patients from the group without highly stenotic lesions presenting with the same clinical findings.

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Reference

1. **Prinzmetal M, Ekmekci A, Kennamer R, et al:** Variant form of angina pectoris. JAMA 174:1794–1800, 1960

SEX DIFFERENCES IN STRESS TESTING—I

Sketch et al.[1] postulate that estrogens may be partly responsible for the high incidence rate of false positive exercise test results in women. The average of their female patients was 50.0 + 8.4 years; presumably all were postmenopausal. It would be of interest to know if the five women with positive stress test and angiographic coronary artery disease were pre- or postmenopausal. Also, what was the age distribution of the 10 women with a positive stress test and negative angiographic findings? Finally, were any of these women receiving substitute estrogen therapy?

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Reference

1. **Sketch MH, Mohiuddin SM, Lynch J, et al:** Significant sex differences in the correlation of electrocardiographic stress testing and coronary arteriograms. Am J Cardiol 36: 169–173, 1975

REPLY—I

Unfortunately, the menstrual history of many of the women we studied is unknown since our study was retrospective. However, it is known that one (20 percent) of the five women with true positive exercise tests was premenopausal and that the other four were postmenopausal and not receiving estrogen. In contrast, 5 (50 percent) of the 10 women with false positive exercise test results were either premenopausal (2 women) or taking estrogens (3 women). The other five women were postmenopausal and not receiving estrogen. These facts do not necessarily explain the high incidence rate of false positive exercise tests in women. If one postulates that false positive exercise tests are caused by estrogen therapy, three of the women with false positive results would have, in fact, had true negative tests had they not been taking estrogen. Hence, only seven women would have had false positive exercise results, and the incidence of false positive results would have been 58 percent which is still significantly higher than that found in men (8 percent).

The mean age of these women with true positive exercise test results was 53 years ± 5.1 which was not significantly different from those with false positive exercise tests (51 years ± 7.3). However, analysis of the women in two distinct age groups is of interest. There were 27 women younger than 50 years (Group A) and 29 women 50 years of age or older (Group B). Twenty-two percent (6 of 27) of group A and 31 percent (9 of 29) of group B had positive exercise test results. The distribution of the positive and negative exercise tests is shown in Table I.

The incidence of positive and negative exercise test results is not significantly different between groups. In women 50 years of age or older the incidence of false positive exercise tests is not significantly different from that found in the total population of women we studied (67 percent) and is considerably greater than in men (8 percent). Below the age of 50 years the incidence rate of false positive exercise tests is extremely high (83 percent), but this may be more apparent than real. This is in part due to the low incidence rate of significant coronary artery disease in this group (11 percent versus 29 percent in Group B), which is not surprising, and which tends to raise the incidence rate of false positive test results by reducing the denominator of the equation from which the incidence is calculated. Further, if one postulates that estrogen therapy is associated with and causes false positive exercise tests, one would expect the incidence rate of false positive tests to be still lower since two women with false positive tests in group A were taking estrogens.

TABLE I

Distribution of Positive and Negative Exercise Tests

Tests	Number and Incidence Rate	
	Group A (27 women)	Group B (29 women)
True positive	1 (17%)	4 (44%)
False positive	5 (83%)	5 (56%)
True negative	19 (90%)	16 (80%)
False negative	2 (10%)	4 (20%)

Although the preceding discussion is of interest, the number of women is too small to draw valid conclusions concerning the cause of the high incidence rate of false positive tests in women, especially those under age 50 years. A postulate is possible, however, with the hope that it will stimulate further investigation.

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SEX DIFFERENCES IN STRESS TESTING—II

The substantial differences Sketch et al. found between men and women in the results of multistage submaximal exercise stress tests are due primarily to the much larger percentage of abnormal patients among the men than among the women in their test population and the effect this has on the variables they used to express their results.

They reported that 55 (89 percent) of 62 men with a positive stress test had 75 percent or greater narrowing of one or more coronary arteries. In other words, if one defines "significant" coronary artery disease as 75 percent or greater narrowing, the conditional probability of significant coronary artery disease being present *given* a positive stress test, denoted p(D+|T+), was about 0.89 for men. Of 15 women with a positive stress test, only 5 (33 percent) had 75 percent or greater narrowing of one or more coronary arteries. In other words, the p(D+|T+) for women was about 0.33. Furthermore, the probability of a patient with a *negative* stress test having significant coronary artery disease was also much less among women than among men. Forty-nine (37 percent) of 133 men with a negative stress test had 75 percent or greater narrowing of one or more coronary arteries. In other words, the conditional probability of significant coronary artery disease given a negative stress test, denoted p(D+|T−), was 0.37 for men. Five (12 percent) of 41 women with a negative stress test had 75 percent or greater narrowing of one or more coronary arteries. In other words, the p(D+|T−) for women was only 0.12.

The large differences between men and women in p(D+|T+) and p(D+|T−) occurred primarily because a much higher porportion of men than women in their test population had significant coronary artery disease (53 versus 18 percent). The p(D+|T+) and p(D+|T−) are extremely sensitive to the proportions of normal and abnormal patients tested. This relation is recognized by Bayes' rule,[2] from which the following expression for p(D+|T+) is derived[3]:

$$p(D+|T+) = \frac{p(T+|D+)\,p(D+)}{p(T+|D+)\,p(D+) + p(T+|D-)\,p(D-)}$$

In this expression, p(T+|D+) is the conditional probability of a positive test, given an abnormal patient, p(T+|D−) is the

conditional probability of a positive test, given a normal patient, and p(D−) and p(D+) are the fractions of normal and abnormal patients respectively in the population being tested. A similar expression may be derived for p(D+|T−).[3] Note that

$$p(T+|D+) = \frac{\text{no. of abnormal patients with positive tests}}{\text{total number of abnormal patients}}$$

and

$$p(T+|D-) = \frac{\text{no. of normal patients with positive tests}}{\text{total number of normal patients}}$$

The p(T+|D+) is the "true positive ratio," or "sensitivity" of the test and the p(T+|D−) is the "false positive ratio."[3]

In contrast to the p(D+|T+) and the p(D+|T−), the p(T+|D+) and the p(T+|D−) are independent of the proportions of normal and abnormal subjects in the tested population. If we determine these latter variables for the series of Sketch et al., we find that there is in fact *no* significant difference in the true positive ratios for men and women and only a small difference in the false positive ratios. There were 104 men with 75 percent or greater narrowing of one or more coronary arteries. Of these, 55 (53 percent) had an abnormal stress test, a true positive ratio of 0.53. There were 10 women with 75 percent or greater narrowing of one or more coronary arteries. Five (50 percent) had an abnormal stress test, a true positive ratio of 0.50. Thus, there is no significant difference between men and women in the conditional probability of an abnormal stress test, given 75 percent or greater narrowing of one or more coronary arteries ($P = 0.97$). There were 91 men without 75 percent or greater narrowing of any coronary artery. Of these, seven (8 percent) had a positive stress test, a false positive ratio of 0.08. There were 46 women without 75 percent or greater narrowing of any coronary artery. Of these, 10 (22 percent) had a positive stress test, a false positive ratio of 0.22. The difference in the probabilities of a normal man versus a normal woman having a positive stress test was small but statistically significant ($P = 0.054$).

In summary, an analysis of the data of Sketch et al. indicates that there is no significant difference between the probabilities of true positive stress tests for men and women with significant coronary artery disease, and only a small difference in the probabilities of false positive stress tests. It would therefore seem premature to conclude that the physiologic responses of men and women to stress are different.

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REPLY—II

Turner's analysis of our data appears to show only a small but statistically significant difference in the probability of false positive exercise tests (as he defines them) between men and women. However, we question the validity or applicability of his approach.

First, the incidence ratio of coronary artery disease is significantly lower in women than in men both in the United States[1] and in our study population. Any postulate or analytical method requiring an equal distribution would require a different and nonexistent situation and, hence, cannot be considered.

Second, the clinician is led to an incorrect conclusion by the method of calculating the ratio or probability of false "positive" results suggested by Turner:

$$P(T+|D-) = \frac{\text{no. of normal patients with positive tests}}{\text{total no. of normal patients}}.$$

In the clinical situation, one is interested in knowing the probability that a "positive" exercise test is not (or is) associated with significant coronary artery disease (that is, is falsely [or truly] "positive") without knowledge of coronary arteriographic studies. Turner's formula does not provide this information. It gives the probability that a patient *known to be normal* has of having an abnormal exercise test. It presumes that the physician has prior knowledge of the absence of disease in his patient. We believe a more appropriate formula is:

$$\text{Incidence of false positive tests} = \frac{\text{no. of patients with false positive tests}}{\text{total no. of patients with positive tests}}.$$

It should be noted that this rationale is applicable to both false "positive" and false "negative" probabilities.

Third, as pointed out by McNeil et al., who are quoted by Turner, Baye's theorum permits one to formulate probability statements as to the presence or absence of disease in a patient who has an abnormal (positive) or normal (negative) diagnostic test. The application of this theorum to our data reveals that the probability that a positive exercise test will be associated with significant coronary artery disease is 0.92 in men and 0.33 in women (an almost threefold difference). Similarly, the probability that a negative exercise test is associated with significant coronary artery disease is 0.36 in men and 0.11 in women (likewise, a threefold difference). Hence, our data support the postulates that (1) despite its low sensitivity, a positive exercise test is useful in confirming the presence of disease in men but is of little value in women, (2) a negative exercise test is useful in ruling out the presence of significant coronary artery disease in women but not in men, and (3) previously published work[2–6] suggesting an important difference in the response of men and women to exercise is correct. Further, since completing our study, we have evaluated another group of men and women relative to other variables related to stress testing results, but incidentally also evaluated the incidence of false negative and false positive test results in both men and women. The incidence rates in this second group were remarkably similar to those reported in our article.

Finally, despite the difference in the incidence of coronary artery disease in men and women both in the United States and in our study population, it is necessary to assess whether the sex differences we found are statistically significant. To achieve this we used the preceding formula and chi square analysis with Yates correction. The results are reported in Table III of our article. Most will agree that $P < 0.001$ represents a highly significant statistical difference and that the chi square method is designed to permit analysis of populations of different size and distribution. Hence, the differences we reported between men and women appear to be real and require an explanation other than that suggested by Turner.

Michael H. Sketch, MD, FACC

Acknowledgment

I thank the Rev. Wm. Sharp, Professor of Mathematics, Creighton University, Omaha, Nebraska for his review of our data and analysis and the analytical approach of Turner.

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REPLY—III

It has been suggested to us in another letter (whose author wishes to remain anonymous) that the incidence of false negative tests might have been lower had we evaluated electrocardiograms recorded during exercise. The following is pertinent: Electrocardiographic tracings were recorded during exercise but their technical quality did not permit accurate analysis of the S-T segment of 1 to 2 mm of S-T segment depression. A technique has now been developed that produces high quality 12 lead electrocardiographic recordings, even when a patient is running rapidly, and the significance of S-T segment changes recorded during exercise will be reported by us shortly. Although it is possible that the incidence of false negative tests might be reduced if one included electrocardiographic recordings made during exercise, the incidence of false positive tests might increase since the degree of S-T segment depression is most often greatest during exercise.

Would maximal stress testing decrease the incidence of false negative exercise test results? The patients we studied with normal coronary arteriograms achieved a mean end-exercise heart rate of 148 ± 8 beats/min which is 83 percent of their mean, maximal predicted heart rate; that is, these patients performed submaximal stress tests. Bruce and Hornsten[1] and Blomqvist[2] have reported that the maximal exercise-induced heart rate is 15 to 22 percent lower in patients with ischemic heart disease than in normal subjects. Patients in our study who had significant coronary stenosis attained a mean end-exercise heart rate of 136 ± 19 beats/min, which is 21 percent lower than the mean maximal predicted heart rate of this group (171 beats/min) had the patients been normal. It may be concluded therefore that our patients with significant coronary artery disease, whether they had true or false positive exercise test results were, in fact, near maximally stressed. Hence, it is doubtful if "maximal" stress testing would have decreased the incidence of false negative exercise tests although it might have increased the number of true or false positive results.

Michael H. Sketch, MD, FACC

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President's Page: A Manpower Problem

The American College of Cardiology finds itself facing a dilemma created largely by its rapid growth. This growth affects both the membership and the programs. As a consequence, and in spite of the large potential manpower pool provided by 7,000 members, individual human resources identified and available to the College for planning and for expansion of current programs and implementation of new programs are relatively few.

In addition to pediatric cardiologists, cardiovascular surgeons and others concerned with heart disease, more than 50 percent of physicians who spend at least half of their professional time in the care of patients with cardiovascular disease and consider themselves adult medical cardiologists are members of the American College of Cardiology. This makeup and the size of our organization coupled with its rapid growth suggest strongly that the College is the major spokesman for the American cardiologist. Because of this leadership position it can no longer concern itself solely with education. To discharge its obligation to the membership, it must extend its current commitment in the legislative area, and become involved with the economics of cardiology. These are important arenas affecting the future of cardiology and the cardiologist.

Furthermore, it is no longer sufficient or wise for the College to respond, even if rapidly, to issues raised by others, issues often initiated by persons who are well meaning but who do not have a clear grasp of the many variables that together constitute cardiology. We must be involved from the onset and have a significant and meaningful input during the planning stages of programs affecting our specialty. At this moment any major expansion of ongoing activities alone would strain our present "working" manpower, to say nothing about a major commitment to the legislative and economic issues.

Currently, some 270 persons serve on College committees. At first glance this number would appear sufficiently large, but this is not the case. The process whereby ideas and concepts result in plans to be implemented by the Board of Trustees and officers is time-consuming and involves sizable groups of people. Furthermore, of the 270 members, many contribute to the idea and planning phase but are unable to take part in the actual implementation of the plans.

Consequently, if we as a responsible group are to commit ourselves in a major and effective way in the legislative and economic areas of cardiology and at the same time maintain our leadership in continuing medical education, we must identify a larger pool of "working" members. This task would appear to be simple for in the very act of becoming a member our 7,000 members have demonstrated a potential for active participation. Yet, in spite of this sizable potential pool, the process of actually identifying the "worker" is complex and difficult. Although your officers make every effort to involve as many members as possible, they alone cannot be expected to know all, or even a majority, of those among you who would work effectively and enthusiastically if asked.

This process of identifying available workers may depend both on your willingness to make yourself known and on the Governors. Obviously, the College could not absorb a sudden influx of large numbers of "volunteers" but, as the programs of which I speak develop, the College will benefit greatly by involving many of you.

Let me stress again that the College, because of its leadership role in the cardiologic community, faces a manpower problem. I believe that an orderly expansion of our program in the years to come is essential if we are to remain a viable and relevant group and maintain our leadership. At the same time I believe that if this expansion is to take place, additional human resources must be identified.

It is up to each of you to come forth, to become involved and to support the activities of your College.

Charles Fisch, MD, FACC
President, American College of Cardiology

Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

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SEPT. 8–10 **Venous Thrombosis Pulmonary Embolus Complex.** Orville Horwitz, FACC and Frank D. Gray, directors and Henry Berkowitz, H. James Day and L. Henry Edmunds, FACC, co-directors. The Hilton Hotel of Philadelphia, Philadelphia, Pa.

SEPT. 13–14 **Exercise Testing in Children and Young Adults.** Frederick W. James and Samuel Kaplan, FACC, directors. Children's Hospital Medical Center, Cincinnati

SEPT. 13–17 **Cardiology for the Consultant.** E. Grey Dimond, FACC and Don R. Santschi, FACC, directors. University of Missouri-Kansas City School of Medicine, Kansas City, Mo.

SEPT. 23–25 **The Clinical Spectrum of Adult Heart Disease.** Jonathan Abrams, FACC, director and Paul T. Cochran, FACC, co-director. Basic Medical Sciences Building of University of New Mexico Health Sciences Center, Albuquerque, N. Mex.

SEPT. 28–30 **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director. Indianapolis Hilton Hotel, Indianapolis, Ind.

OCT. 11–13 **Electrocardiography: Core Curriculum and Self-Assessment.** Leonard S. Dreifus, FACC, director. University City Holiday Inn, Philadelphia, Pa.

OCT. 11–13 **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC and Borys Surawicz, FACC, directors. Indiana University Medical Center, Indianapolis, Ind.

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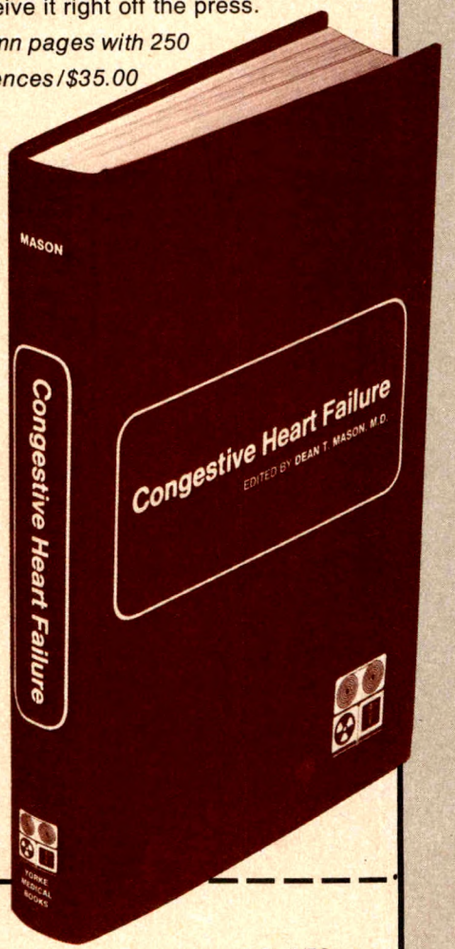

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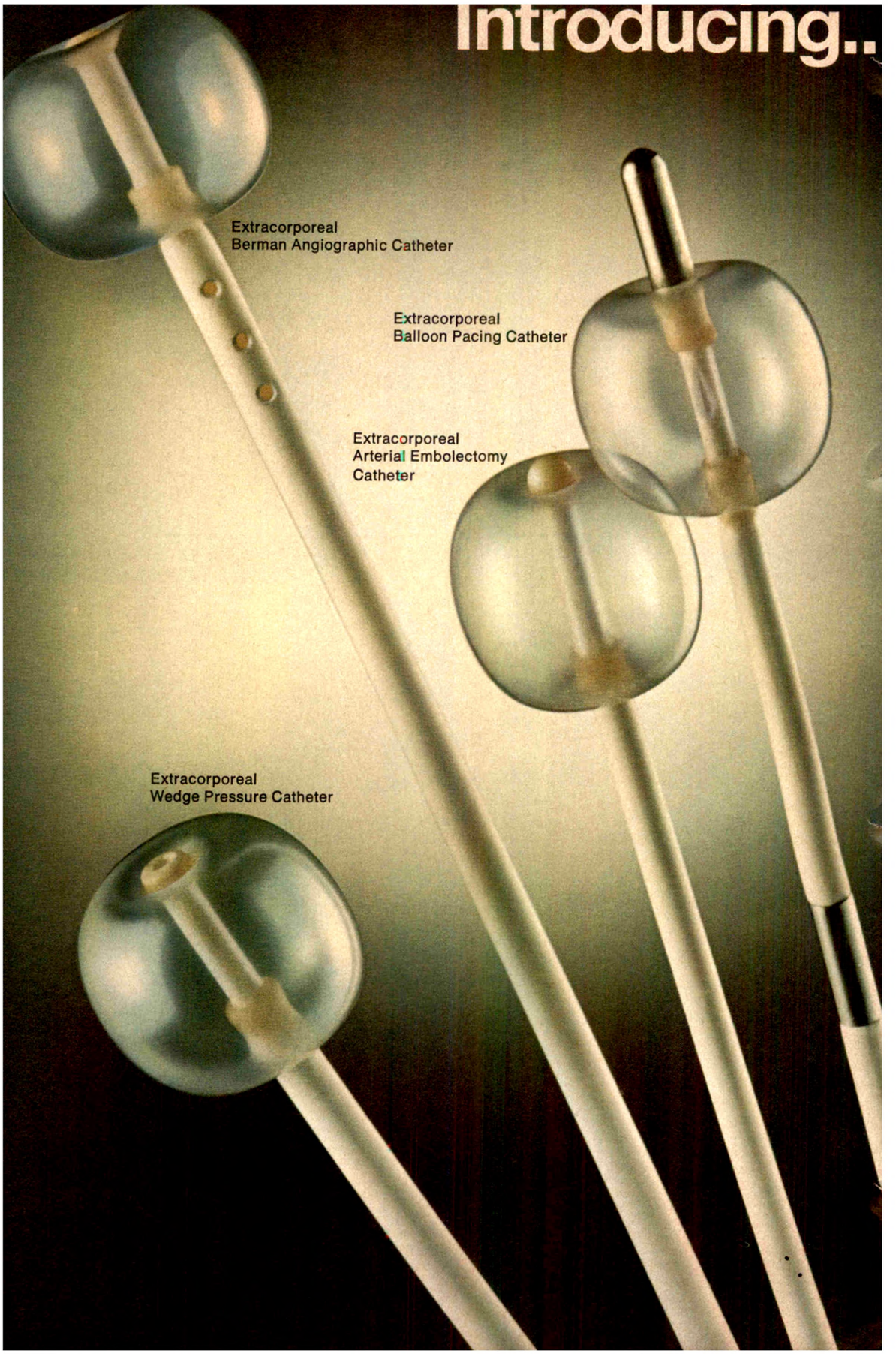
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Also Available: The New Extracorporeal Stylet Pacing Catheter. Designed with a soft flexible catheter body and removable stylet to help minimize the chance of perforation and accidental repositioning after placement.

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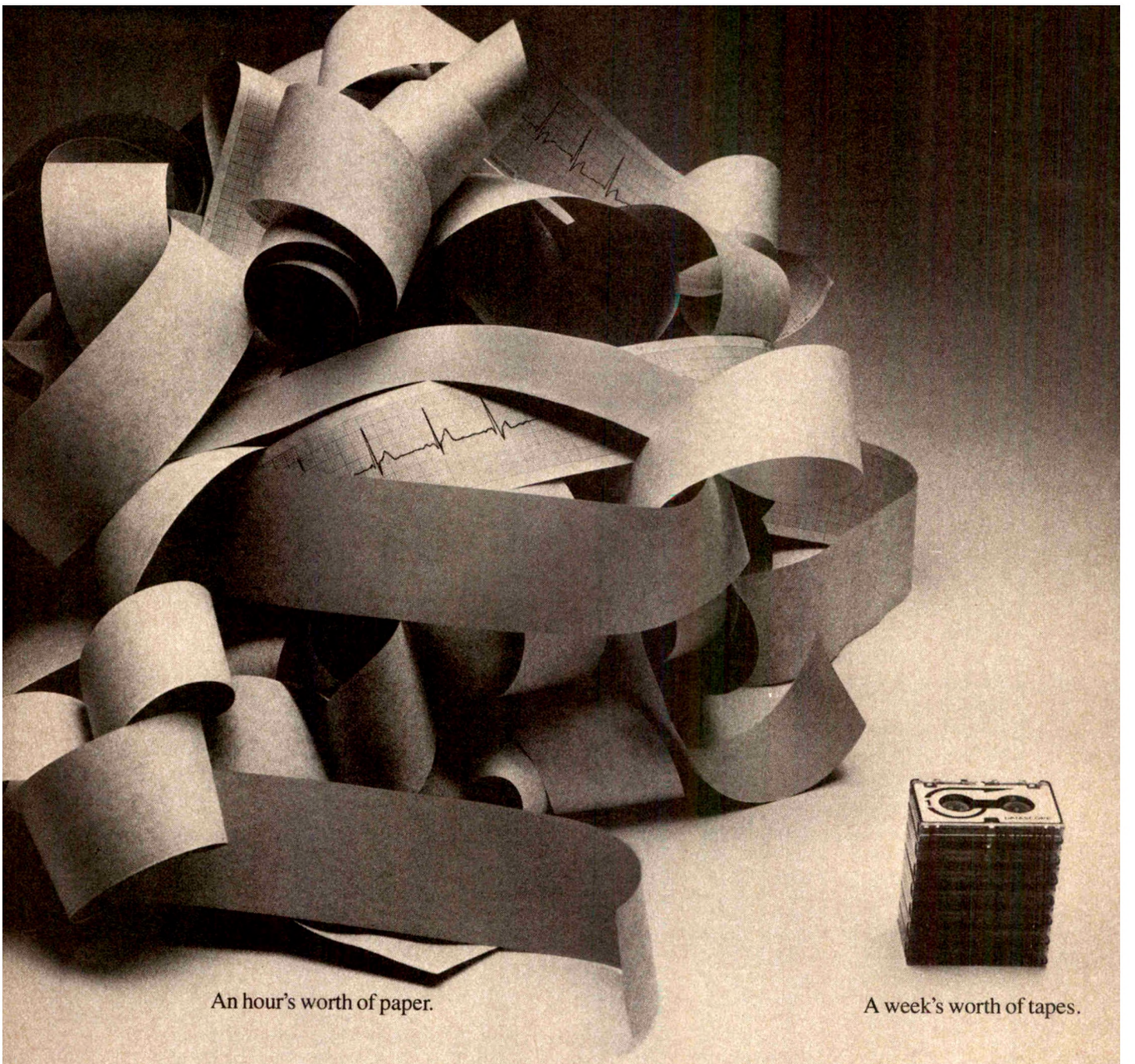
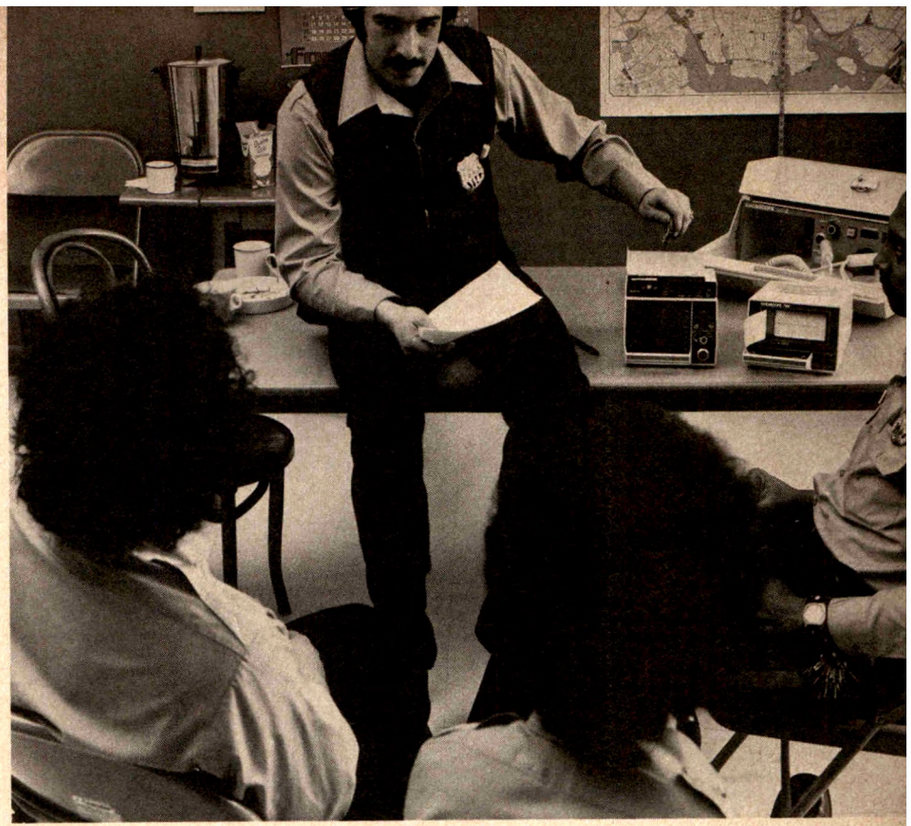


An hour's worth of paper.

A week's worth of tapes.

THE M/D2 NOW HAS A DATABANK™. IT DOES WHAT PAPER NEVER COULD.



For all its advantages, the writer has always had distinct disadvantages. We just invented a tool that does everything the writer does without these hardships.

We call it the Databank.

What the Databank is, in fact, is a miniaturized cassette recording system that integrates into the M/D2.

What it does is record the ECG on magnetic tape.

But Databank does more than that. It also allows you to note the management of a patient verbally onto the tape. So you can keep a running record of vital signs, drug therapy and any other pertinent data.

None of which the paper strip could ever provide for.

With Databank, you don't have the bulk or the mess of paper. You can record an hour's worth of data on one small cassette.

And you won't find yourself having to turn the machine on and off as with a writer.

And when it's time to store your records, they fit neatly into a fraction of the space that paper takes.

Most important, since you've recorded the entire procedure instead of a fraction of it, and since you've been able to note all other important data, you can use Databank as a powerful teaching tool. To say nothing of the fact that it's a more viable legal document.

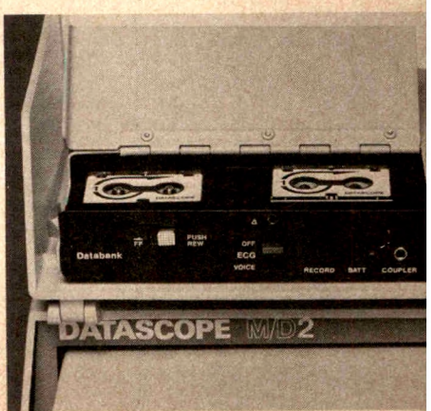
Naturally, when you want a paper record you can have it as well. You simply feed Databank's signal into the Datascope 790 writer and come out with a paper strip. Only instead of having to carry a writer out to the patient, you can leave the 790 on the rescue vehicle or back at the hospital, and transcribe only what you need.

The last advantage of the Databank is the most obvious. It weighs a fraction of what a writer does. And it attaches to either the M/D2 case or to the scope itself.

It makes the M/D2 the most portable and complete rescue system in the world.

We've often said that the M/D2 was the most flexible system you could possibly own. Today, it's more so.

For further information about our new model 770 Databank, write Datascope Corp., 580 Winters Ave., Paramus, N.J. 07652.



THE DATASCOPE M/D2 DATABANK

Now...2 ways to make orange juice really effective K^+ therapy

And supply the chloride most patients need with potassium supplementation.

Potassium—"rich" orange juice actually contains only about 1 meq per ounce. To reach effective maintenance levels, your patients would have to drink 40 or more ounces of orange juice a day.

But now, new orange-flavored Kay Ciel Elixir and Kay Ciel Powder mix tastily with your patient's morning juice; one tablespoon Kay Ciel Elixir or one Kay Ciel Powder packet supplying 20 meq of potassium and of chloride—about four times the K+ in a glass of orange juice alone.

Repeat in the evening for a full therapeutic regimen. Or, if you want your patient to avoid the extra calories, new orange-flavored Kay Ciel Elixir and Kay Ciel Powder taste great in 4 ounces of water.

Improve patient compliance by prescribing the KCl they need...in a way they'll like.

CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps and hyperkalemia.

WARNINGS: Do not use excessively.

PRECAUTIONS:

PATIENTS SHOULD BE CAUTIONED TO ADHERE TO DILUTION INSTRUCTIONS.

ADVERSE REACTIONS: Potassium intoxication indicated by listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac depression, arrhythmias, arrest and heartblock. Vomiting, nausea, abdominal discomfort and diarrhea may occur.

145-4

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New Orange-Flavored Kay Ciel®

Elixir
potassium chloride 10%
(20 meq/15 ml)

Powder
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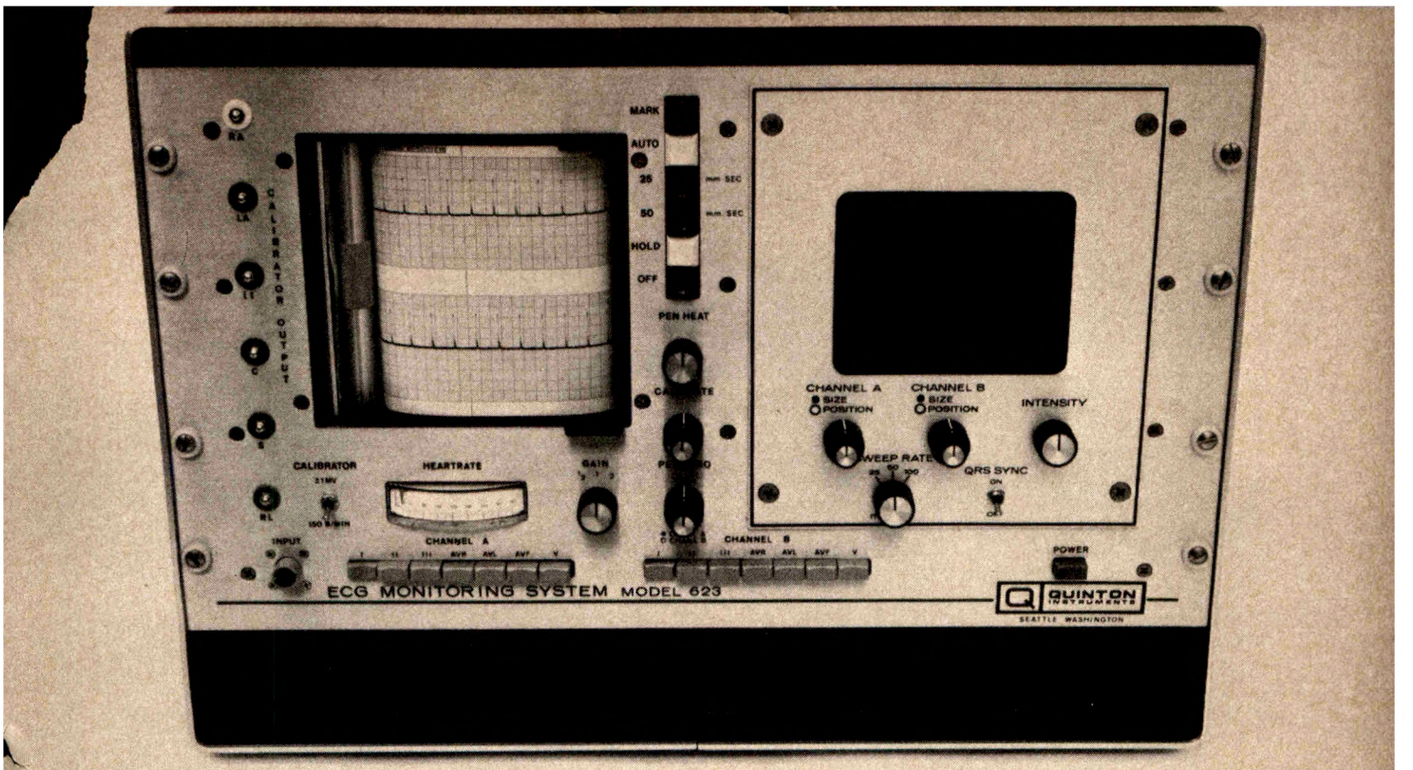
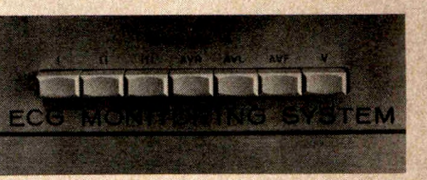
(20 meq/packet)

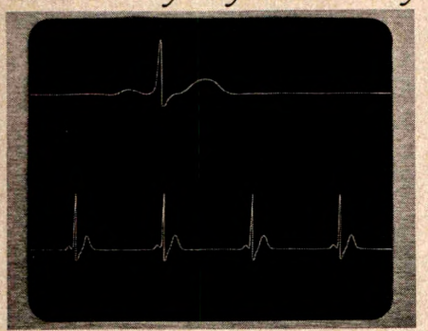


Quinton introduces a practical solution to multi-channel ECG.

Quinton's new two-channel exercise ECG system is designed for the practical, clinical physician. It combines the advantages of multi-channel ECG and the traditional simplicity and everyday durability of Quinton design.



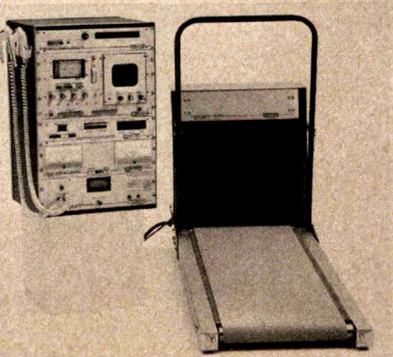
Pushbutton lead selection. Display and record any two leads simultaneously. Switch leads instantly by simply pushing a button.



With the QRS Sync feature, each consecutive QRS complex can be expanded to the full width of the screen. It allows you to detect even the tiniest fluctuations in wave pattern.

Improved system calibration. Most ECG systems only offer internal standardization of the recorder. The Quinton calibration system not only checks the recorder, it checks the oscilloscope, patient cables and heart rate meter. It assures you of total system accuracy.

No battery packs required. Our new, lightweight patient cables eliminate the need for battery packs and reduce motion artifact to a minimum. For details, contact Quinton Instruments, Dept. E-75, 2121 Terry Avenue, Seattle, Washington 98121.



Quinton stress test systems—as reliable as our treadmills.

Fat chance.

Cardiologists and Internists know the pattern of post-MI "good intentions" all too well. When a cardiac patient starts feeling better, all the years of good living and bad habits creep back into his lifestyle. And his chance for an active, healthy future shrinks as his waistline expands.

It's a problem of conditioning and your good counsel alone may not be enough to break the habits of a lifetime.

But a Cardiac Treatment Center© can.

A CT Center is a professionally staffed, fully equipped unit which develops the new, healthy habits you prescribe for your patient and conditions your patient so those new habits become a permanent part of his daily routine.

Cardiac Treatment Centers,* directed by physicians, improve the quality of life for heart attack victims and post surgical patients through physician-prescribed exercise therapy monitored by advanced telemetry systems and supervised by Nurse-Therapists.

A typical CT Center staff consists of one or more Nurse-Therapists and a secretary. The CT Center is supervised by a local physician (cardiologist or internist). A regional CT Center coordinator helps to maintain the uniformly high professional standards followed by CT Centers across the country.

From your patient's point of view the most important staff members are the Nurse-Therapists. They are R.N.'s with at least one year CCU experience (or equivalent). They undergo a rigorous 3-week, 120-hour course which equips them to manage every aspect of the CT Center program – from stress testing to emergency procedures.

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There are now more than 75 Cardiac Treatment Centers located across the nation. They are recognized for reimbursement of their services by major health insurance companies, Blue Cross and government agencies.

For further information, write to Cardiac Treatment Centers, c/o Rehab Hospital, 4950 Wilson Lane, Mechanicsburg, PA 17055. Or call 717-697-8211.

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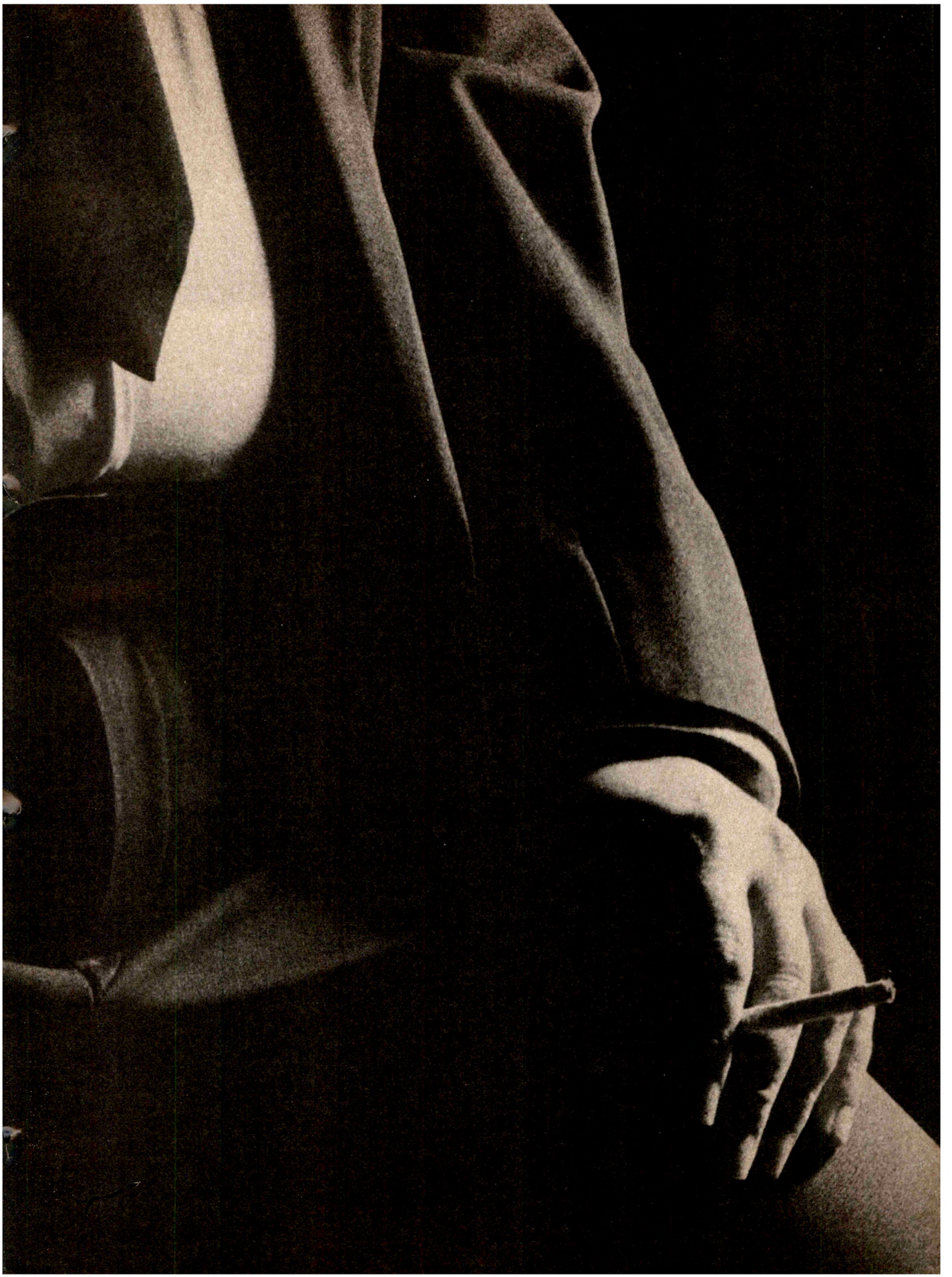

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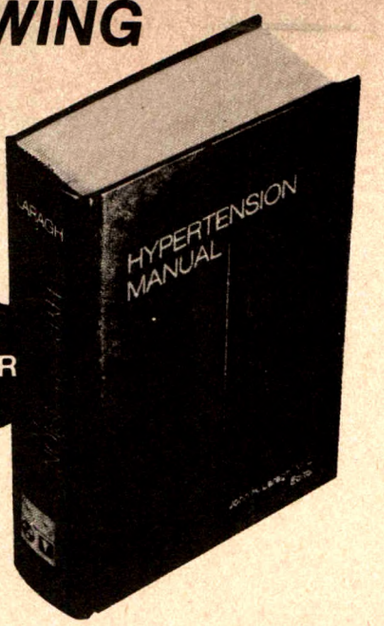

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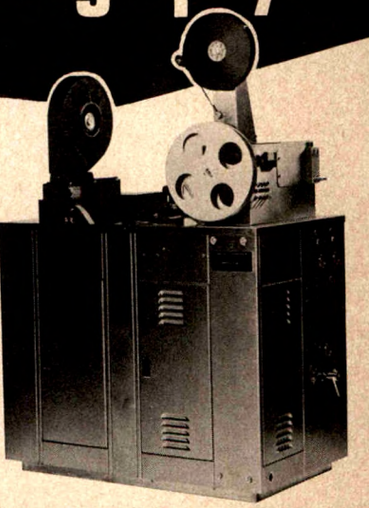

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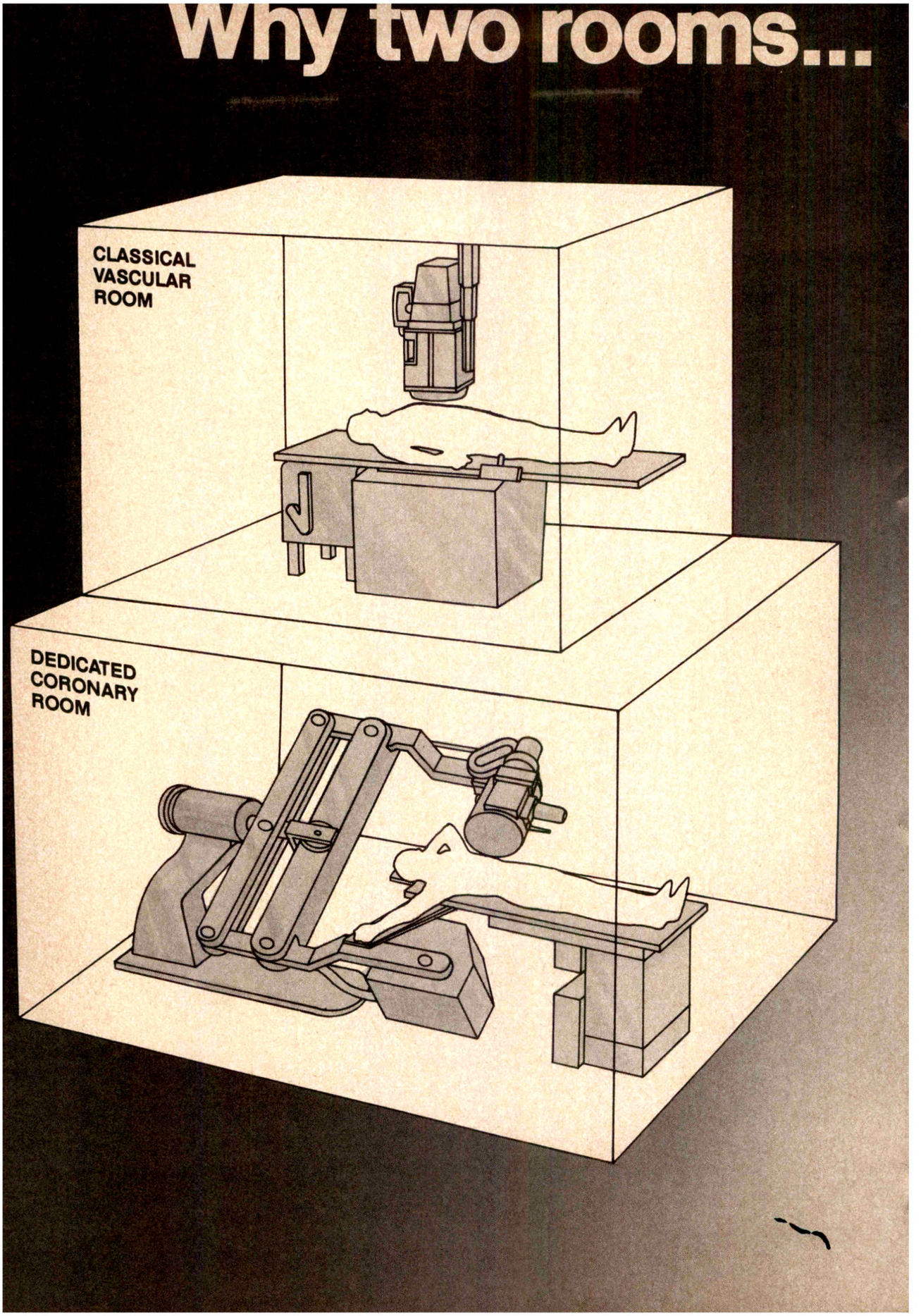
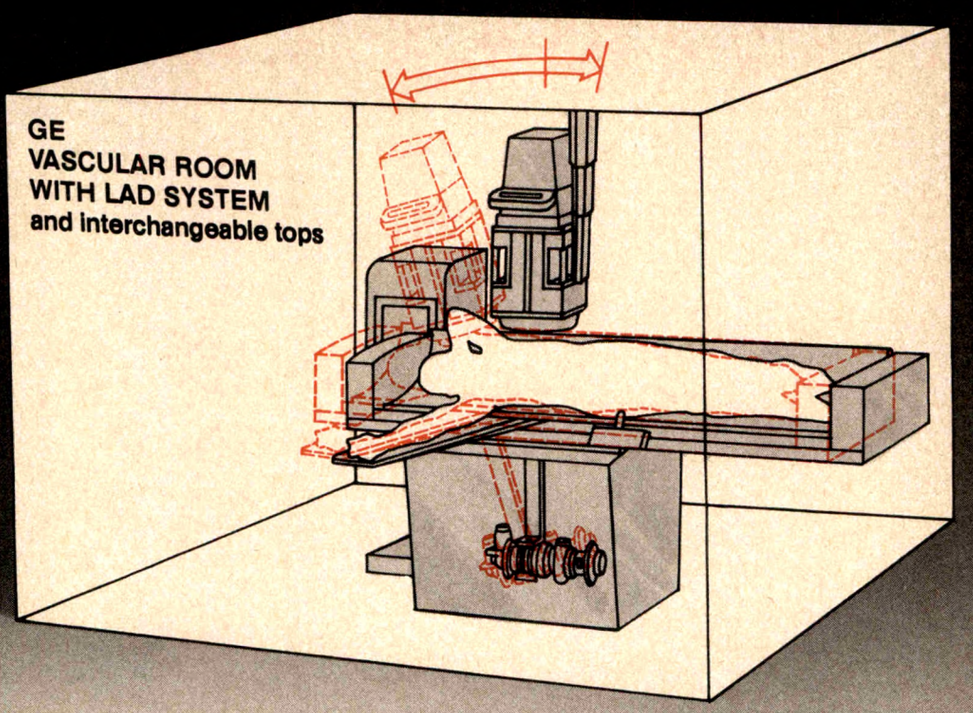


when one does it all?



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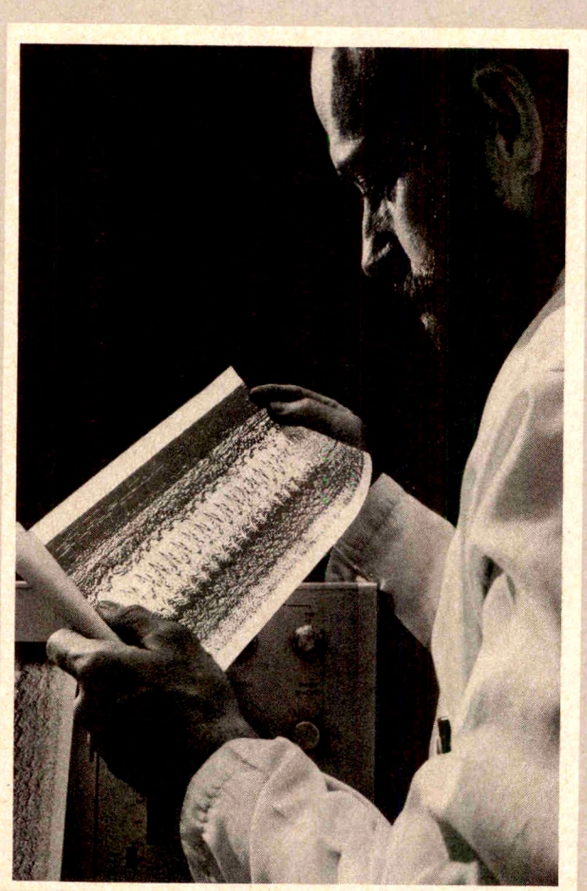

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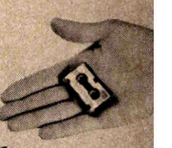
New! Ambulatory Blood Pressure Recorder.



Smaller, lighter compact one-piece unit weighs 25 ounces.

The Remler patented Ambulatory Blood Pressure Recorder has been in use for more than ten years by leading physicians and research institutions throughout the world.

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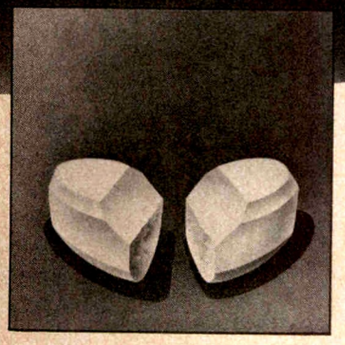

One press of a finger solves two problems

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(isosorbide dinitrate)

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
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Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

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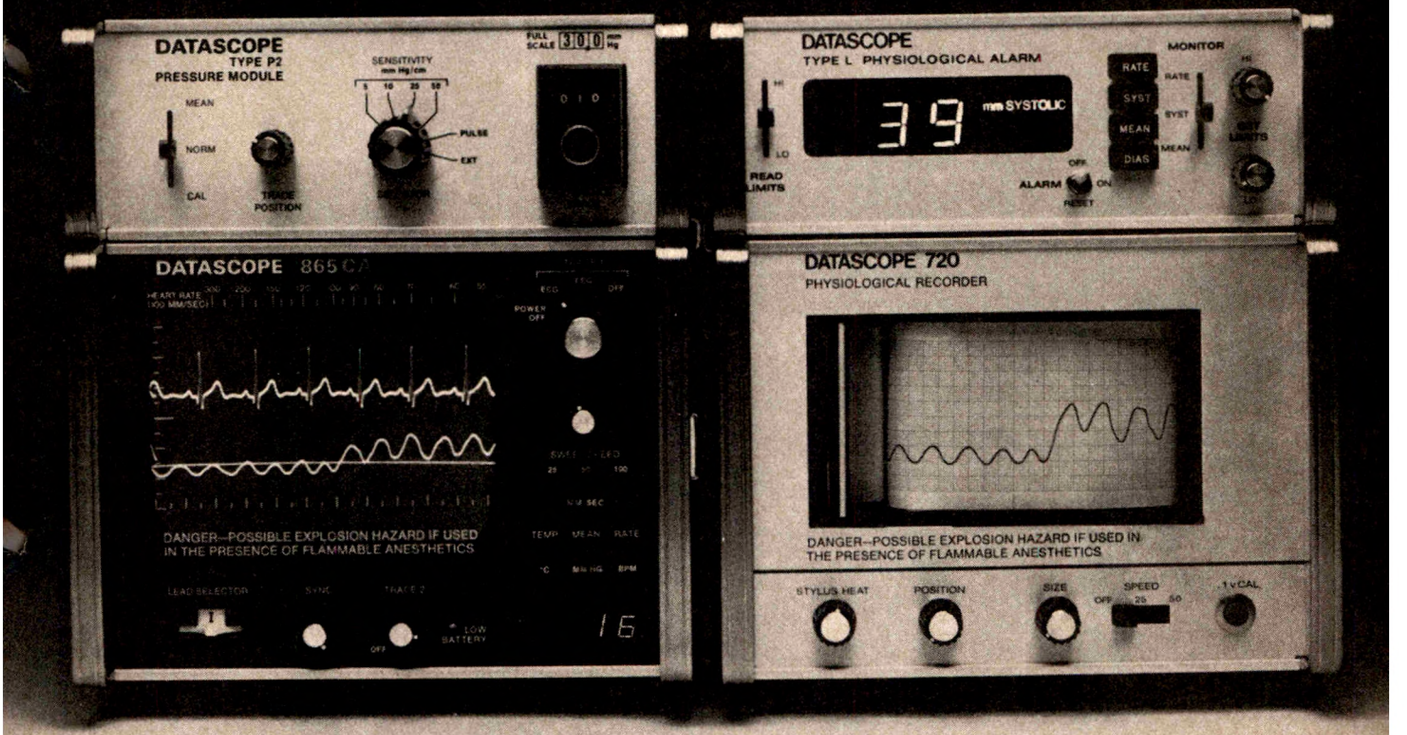

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The Datascope Wedge Pressure Group can simplify your job at the bedside even more.

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If you've gotten used to big, bulky monitoring equipment, our wedge pressure group will come as a pleasant surprise. It's extremely light, and compact. It easily fits at bedside.

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So you don't have to have a unit for every bed.

Which not only makes life simpler for the people who use it, but also for the people who buy it.

For more information on the Datascope Wedge Pressure Group, write: Datascope Corp., 580 Winters Ave., Paramus, N.J. 07652.

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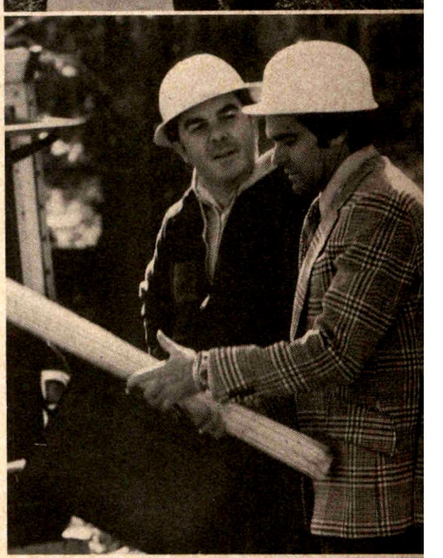
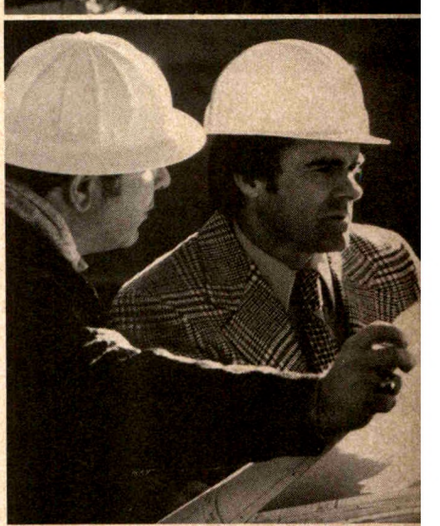
AN ANTIHYPERTENSIVE FROM AYERST

the "healthy" hypertensive





It may be years before he experiences a single symptom of hypertension. But left untreated, even mild to moderate elevations of blood pressure may quietly strip years from an otherwise healthy and active life. Early control with DIUCARDIN may help forestall damage to healthy target organs.

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diuretic/antihypertensive

(See prescribing information on next page.)

For the "healthy" hypertensive, early control with

Diucardin® TABLETS (hydroflumethiazide)

a diuretic-antihypertensive agent

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ACTIONS: The primary action of the thiazide diuretics is to produce diuresis by increasing the renal excretion of sodium and chloride. They inhibit the mechanism for tubular reabsorption of sodium and chloride by direct action on the distal segment. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.

The mechanism(s) of the antihypertensive action of the thiazides has not been elucidated.

INDICATIONS: DIUCARDIN is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis and corticosteroid and estrogen therapy.

DIUCARDIN has also been found useful in edema due to various forms of renal dysfunction as: nephrotic syndrome; acute glomerulonephritis; and chronic renal failure.

Diuretics are indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effect of other antihypertensive drugs in the more severe forms of hypertension.

CONTRAINDICATIONS: Anuria, oliguria.
Hypersensitivity to DIUCARDIN or other sulfonamide derivatives.

The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS: Use with caution in severe renal disease since thiazides may precipitate azotemia. Effects due to accumulation of the drug may occur in patients with impaired renal function.

Use with caution in patients with impaired hepatic function or progressive liver disease since minor changes of fluid and electrolyte balance may precipitate hepatic coma.

Use with caution when hydroflumethiazide is administered in conjunction with other antihypertensive agents. Lowering of dosage of these agents is usually indicated. Thiazides potentiate ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy and During Lactation: Thiazides cross the placental barrier and also appear in breast milk. Consequently, they may cause fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions. Therefore, the potential benefits of thiazide administration in women of childbearing age must be weighed against the possible hazards to the fetus or child.

PRECAUTIONS: Tests should be made at appropriate intervals to detect possible electrolyte imbalance, *i.e.* hypokalemia, hyponatremia, and hypochloremic alkalosis. All patients taking thiazides should be observed for signs and symptoms of electrolyte or fluid imbalance, namely dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Serum and urine electrolyte determinations are particularly important if the patient is vomiting excessively or receiving parenteral fluids.

If hypokalemia should develop, dietary potassium supplementation or the use of dilute potassium solutions should be tried. Small bowel lesions have been reported following the administration of enteric coated, concentrated preparations of potassium salts.

Dilutional hyponatremia may occur in edematous patients during hot weather. Water restriction rather than administration of salt is appropriate except in rare cases when hyponatremia is life-threatening. In actual salt depletion, appropriate replacement should be given.

Hypochloremia is generally mild and usually does not require specific treatment except under extraordinary circumstances, as in renal or liver disease.

The possibility of development of electrolyte or fluid imbalance is increased by brisk diuresis, severe liver disease, or concomitant administration of medications such as digitalis, ACTH, and corticosteroids.

Adequate oral intake of electrolytes should be maintained to minimize the possibility of electrolyte imbalance.

If a progressive increase in serum nitrogen occurs, a careful appraisal of the patient's condition should be made to determine whether diuretic therapy should be continued.

Because of the possibility of hypokalemia developing, patients taking digitalis should be followed carefully since a decrease in body potassium may necessitate lowering digitalis dosage.

Plasma uric acid levels may be increased and could, in susceptible patients, precipitate an attack of gout.

Thiazides alter carbohydrate metabolism. Patients who have diabetes mellitus or are suspected of being prediabetic should be followed closely since hyperglycemia and glycosuria may occur. Dosage adjustment of antidiabetic agents is frequently indicated.

Thiazides may decrease serum PBI without signs of thyroid disturbance.

Thiazides act to decrease the response of the peripheral arterial system to catecholamines and to enhance the effects of curare and its derivatives. Caution should be exercised in administering general anesthesia or curare derivatives to patients taking thiazides.

The antihypertensive effect of thiazides may be enhanced following sympathectomy.

ADVERSE REACTIONS: **Gastrointestinal:** anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, acute pancreatitis.

Central Nervous System: dizziness, vertigo, headache, paresthesias, xanthopsia, restlessness.

Hematologic: leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

Allergic: purpura, photosensitivity, rash, urticaria, necrotizing angiitis, exfoliative dermatitis, glomerulonephritis, intrahepatic cholestatic hepatitis.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Musculoskeletal: muscle cramps, weakness.

Clinical Laboratory Test Findings: electrolyte imbalance, elevation of serum nitrogen, elevation of plasma uric acid, hyperglycemia and glycosuria, decreased serum PBI levels.

DOSAGE AND ADMINISTRATION: **Usual adult dosage:** 50-100 mg. per day.

The dosage regimen should be individualized to obtain the maximum effect at the lowest dosage level. Dosage regimens using 25 mg. DIUCARDIN (hydroflumethiazide) may be adequate in some cases. Dosage should not exceed 200 mg. per day.

HOW SUPPLIED: DIUCARDIN—No. 702—Each scored tablet contains 50 mg. hydroflumethiazide, in bottles of 100 and 1,000.

References: 1. A.M.A. Drug Evaluations, ed. 2, Acton, Massachusetts, Publishing Sciences Group, Inc., 1973, p. 70. 2. Blagg, C.R.: Hydroflumethiazide, a new oral diuretic, Lancet 2:311 (Sept.) 1959.

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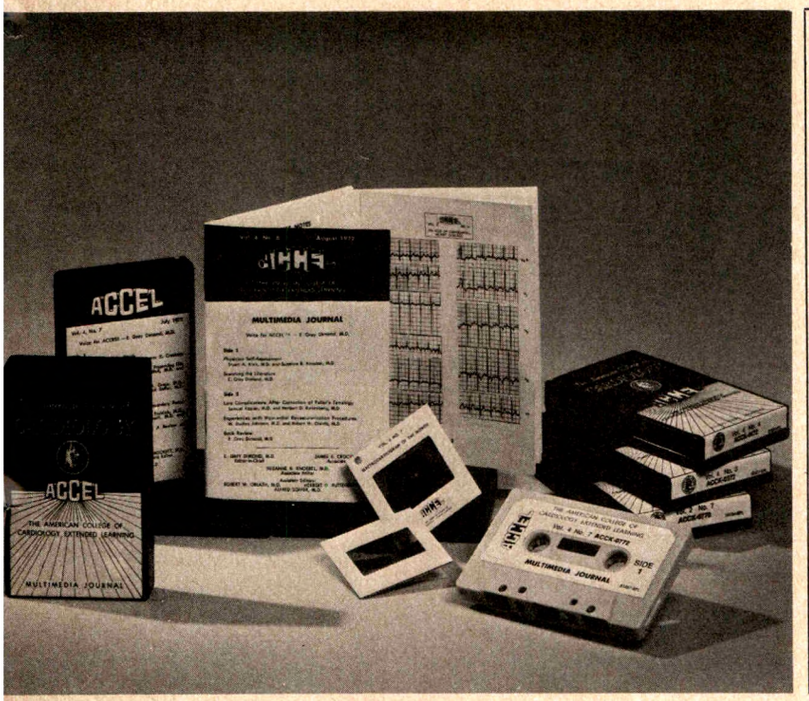

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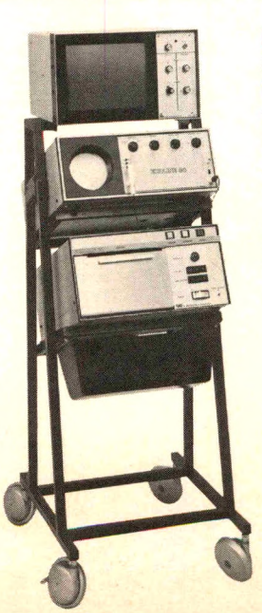

If you would like more details about the new Ekoline 21 and the SKI Echo System, call or write: Smith Kline Instruments, Inc., Dept. U, 880 W. Maude Avenue, Sunnyvale, CA 94086. (408) 732-6000.

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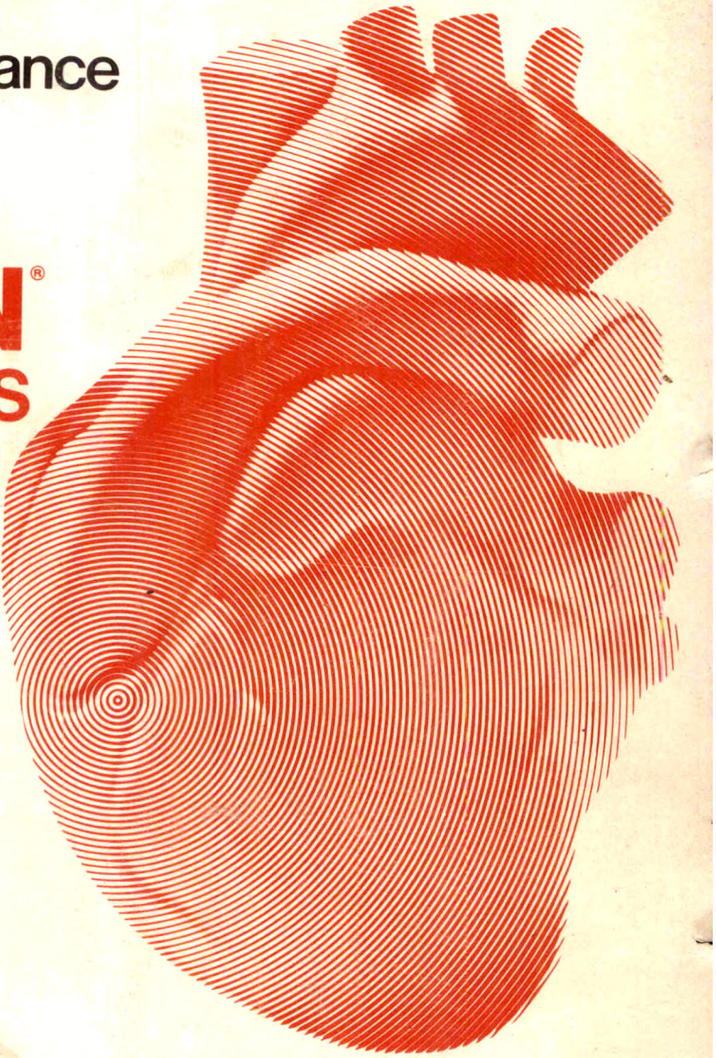
The Pacekeeper™

For the broad spectrum of cardiac arrhythmias broad-range treatment... conversion and maintenance



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TABLETS
(quinidine polygalacturonate)

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- ☐ Convenient B.I.D. or T.I.D. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases.

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*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

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AUGUST 1976

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Treatment of Cardiac Arrhythmias

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Call for Abstracts: ACC 26th Annual Scientific Session Philadelphia, February 28 to March 3, 1977

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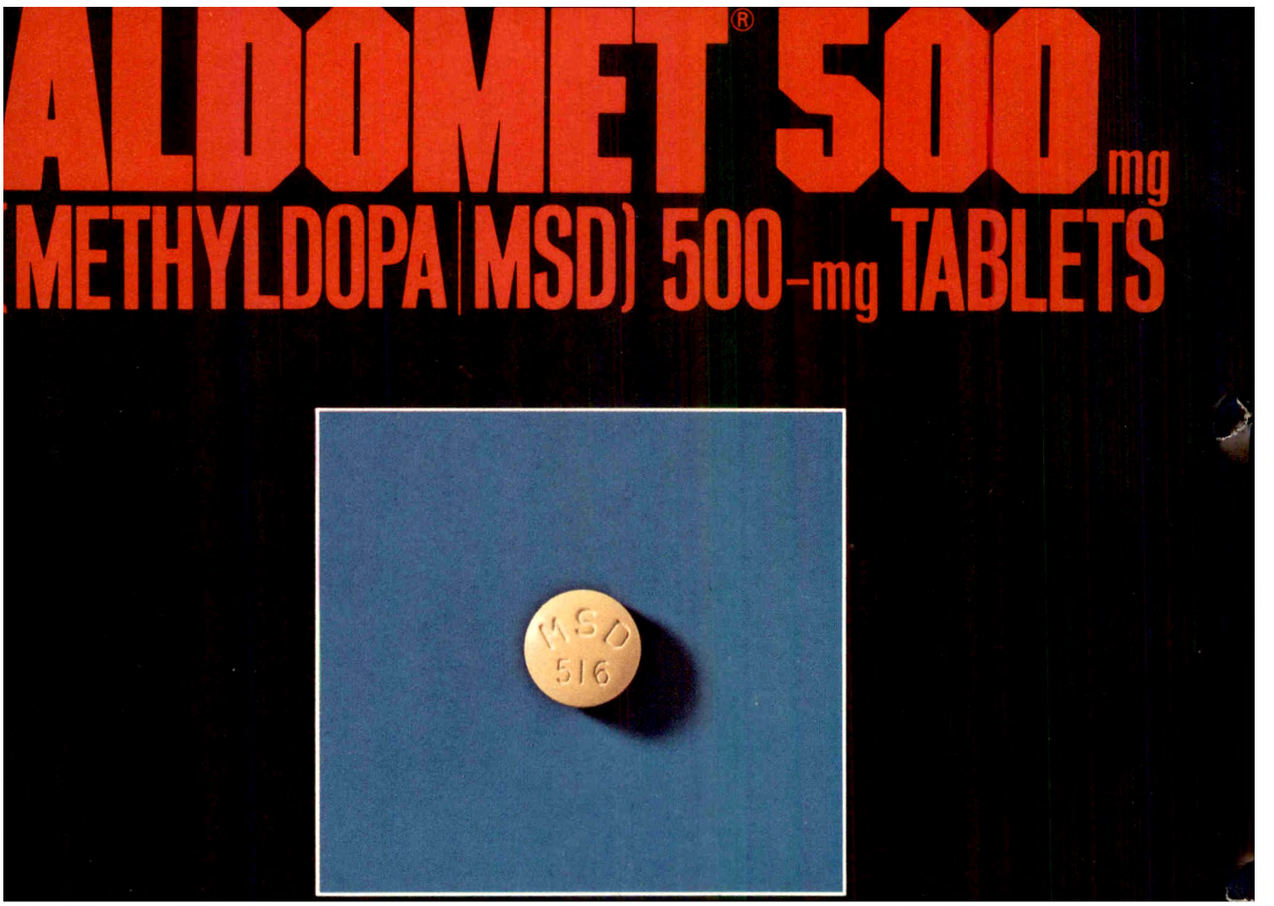
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METHYLDOPA (MSD) 500-mg TABLETS
MSD
516

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ALDOMET (Methyldopa, MSD) is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

For more details see the brief summary of prescribing information.

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

in hypertension

TABLETS: 250 mg, 500 mg, and 125 mg

ALDOMET®

(METHYLDOPA | MSD)

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia.

Allergic: Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third month of therapy; increased dosage or adding a thiazide frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

addendum

MSD MERCK SHARP & DOHME

DOSAGE INFORMATION ON ALDOMET® (Methyldopa | MSD)

Adults

initiating therapy

- 250 mg b.i.d. or t.i.d. the first 48 hours
- increase or decrease, preferably at intervals of not less than two days, until response is adequate
- start dosage increases in the evening to minimize sedation
- adjusting dosage may prevent morning hypotension without losing control of afternoon blood pressure
- when ALDOMET is added, the dosage of thiazides need not be changed
- when given with antihypertensives other than thiazides, the dose of these agents may have to be adjusted and the starting dosage of ALDOMET should be limited to 500 mg daily in divided doses

maintaining therapy

- usually 500 mg to 2.0 g daily in two to four doses
- maximum recommended daily dose is 3.0 g
- occasional tolerance may occur, usually between the second and third month of therapy; adding a diuretic or increasing the dosage of ALDOMET frequently restores effective control
- patients with impaired renal function may respond to lower doses; syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease and may be avoided by lower doses

Children

- initial dosage is based on 10 mg/kg of body weight daily in two to four doses
- increase or decrease daily dosage until adequate response is achieved
- maximum dosage is 65 mg/kg or 3.0 g daily, whichever is less

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As with all quinidine preparations, the titrating of the exact quinidine dosage will vary with each individual patient. With the dosage regimen of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythm.

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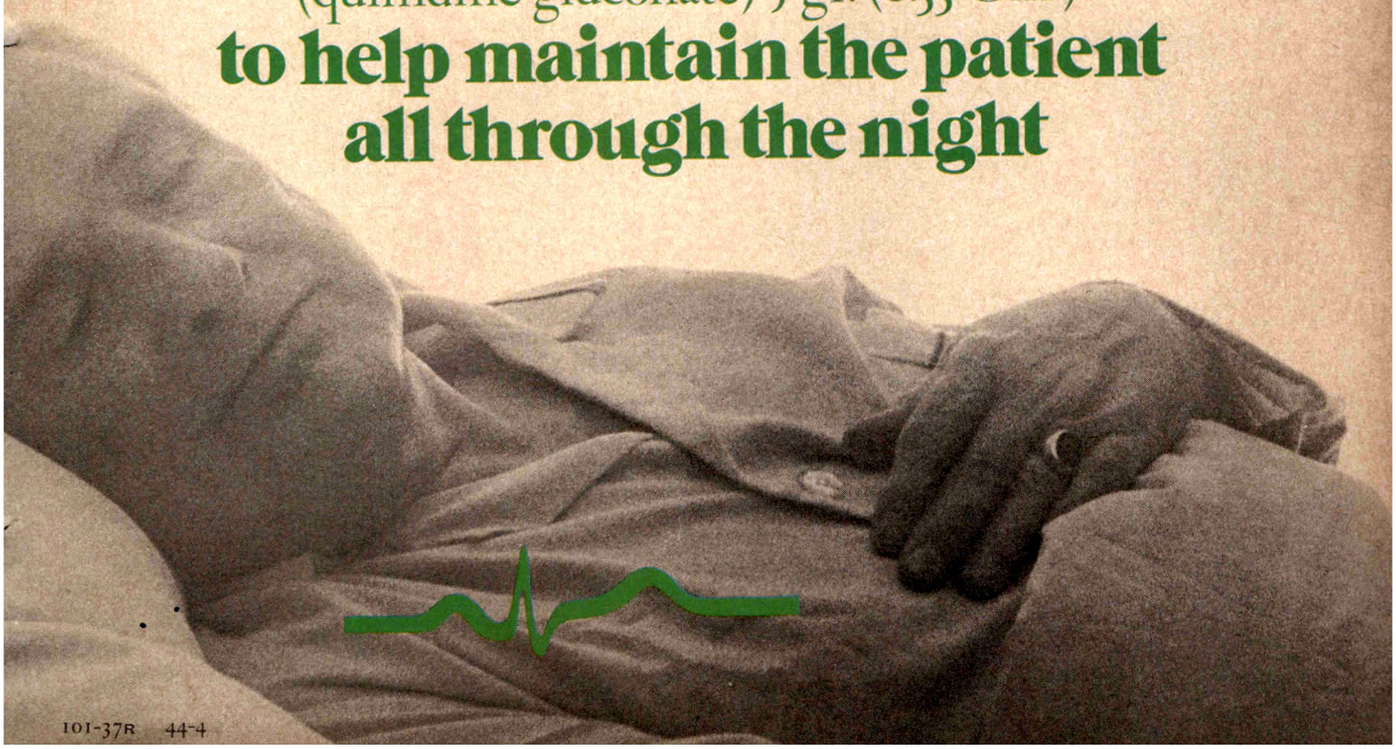

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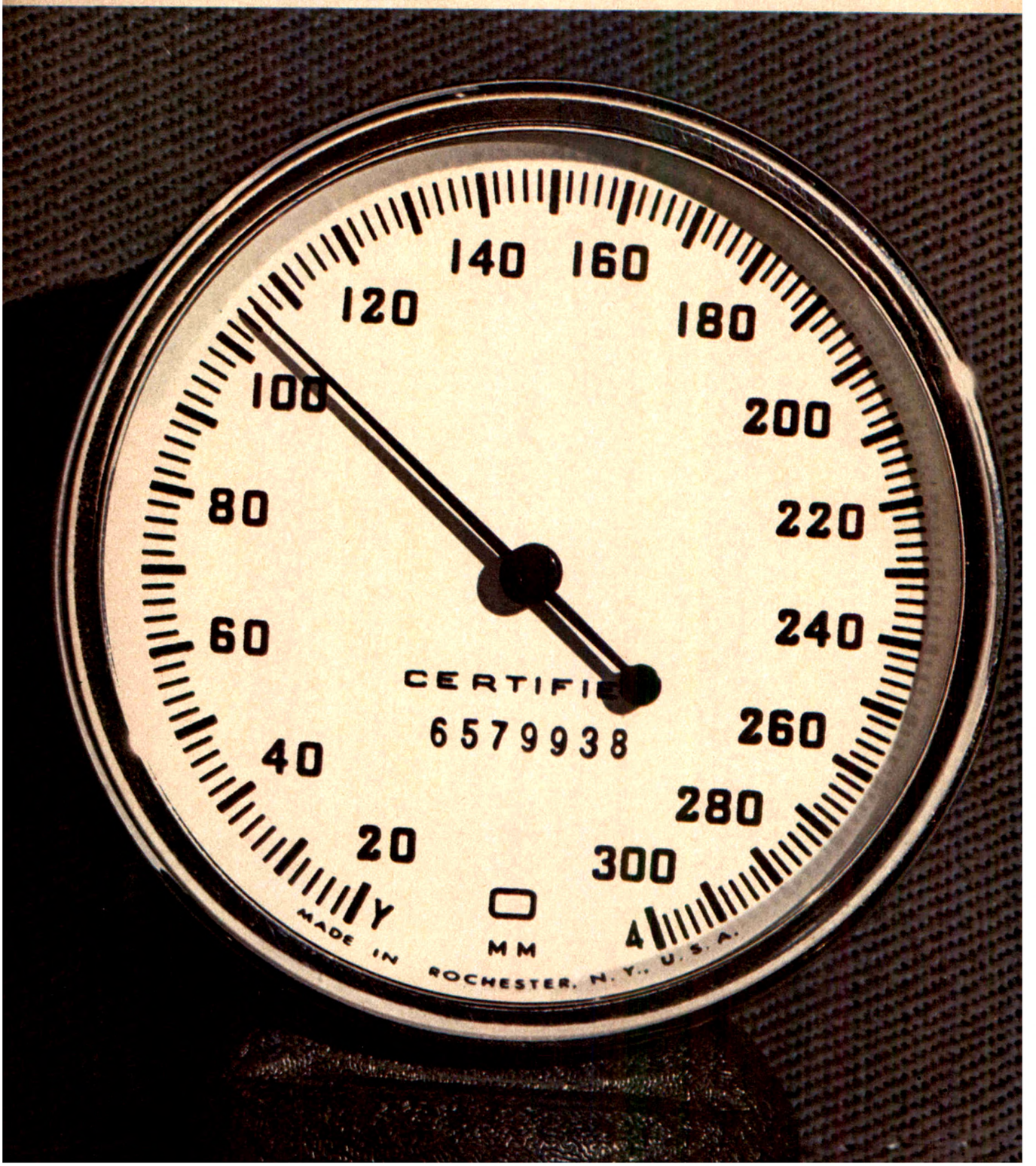

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Particularly in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Elevated serum potassium levels can occur because of the potassium-sparing effect of 'Dyrenium', but they are rare in patients with normal renal function. If hyperkalemia develops, substitute a thiazide alone.

Use 'Dyazide' with caution during pregnancy or in women who might bear children; potential benefits should be weighed against possible hazards to the fetus.

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*'Dyazide' is not indicated for initial therapy. See next page for indications and brief summary of prescribing information.

A9

DYAZIDE®

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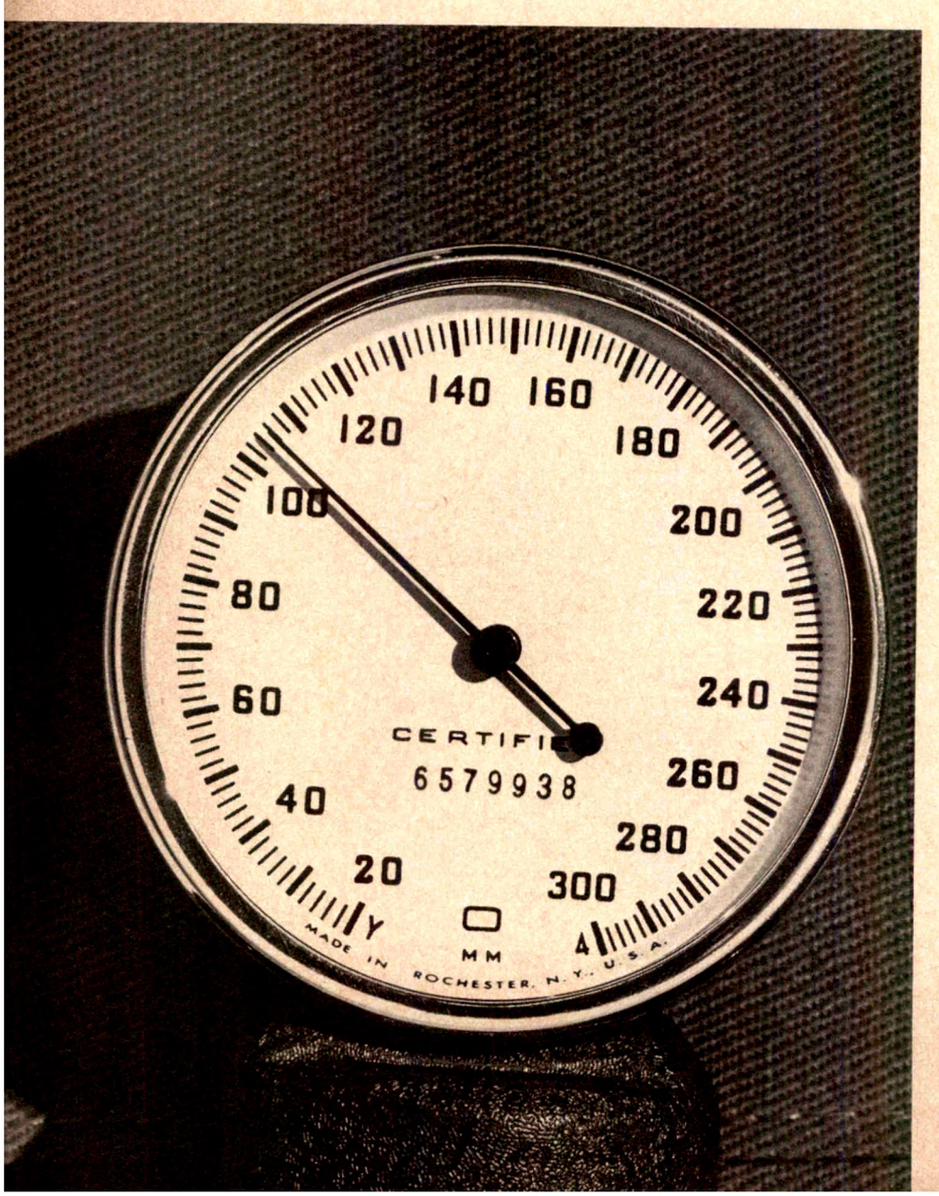
IN HYPERTENSION

- CONVENIENT
- ECONOMICAL



Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **Warning**
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently** — both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

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AUGUST 1976

The American Journal of CARDIOLOGY®

VOLUME 38

NUMBER 2

CONTENTS

CLINICAL STUDIES

141 Frequent Complex Ventricular Ectopy in Apparently Healthy Subjects. A Clinical Study of 25 Cases

HAROLD L. KENNEDY and STEPHEN J. UNDERHILL

This comprehensive study of 25 asymptomatic apparently healthy subjects with frequent or complex ventricular ectopy of 1 to 3 years' duration revealed normal cardiac status in 18 and mild or suspected abnormalities in 7. The ventricular ectopy was predominantly of right ventricular origin and nearly always disappeared during maximal exercise stress testing. Antiarrhythmic drug therapy was generally ineffective. This is a clinical syndrome whose etiology and natural history remain undefined.

149 Sinus Bradycardia and Atrial Fibrillation Associated With the Wolff-Parkinson-White Syndrome

LEONARD S. DREIFUS, HEIN J. WELLENS, YOSHIO WATANABE, DIMITRIOS KIMBIRIS and RAYMOND TRUEX

This study of 33 patients with atrial fibrillation associated with the Wolff-Parkinson-White (WPW) syndrome found sinus nodal disease responsible for the sinus bradycardia (less than 40/min) in 7 patients. Ventricular fibrillation or functional cardiac arrest was documented in four instances. One patient who died from ventricular fibrillation had three anomalous pathways; most of the sinoatrial node was replaced by collagen elastic fibers and there was widespread destruction and fibrous tissue replacement of the atria. Precise electrophysiologic studies should be done and pharmacologic or surgical management, or both, carried out to prevent sudden death in such patients with short refractory periods associated with atrial fibrillation and the WPW syndrome.

157 Long-Term Evaluation of Early Repolarization Syndrome (Normal Variant RS-T Segment Elevation)

HIROFUMI KAMBARA and JOHN PHILLIPS

Electrocardiographic features of the "early repolarization syndrome" in 65 patients included (1) persistent upward concave elevation of the RS-T segment with distinct or embryonic J waves, and slurred downstroke of R waves or distinct J points, or both; (2) RS-T segment elevation in the precordial leads; and (3) rapid QRS transition in the precordial leads with counterclockwise rotation. Eight patients presented with "labile" or juvenile T wave patterns. These changes may simulate pericarditis and myocardial ischemia or hypertrophy.

Continued on page A17

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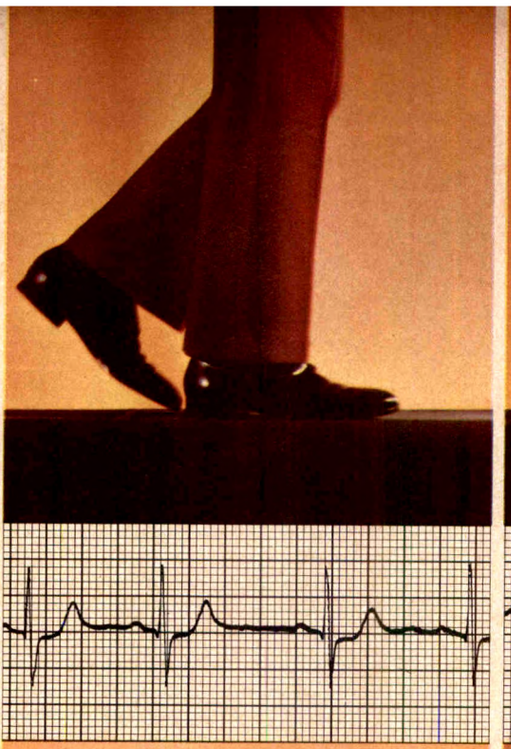

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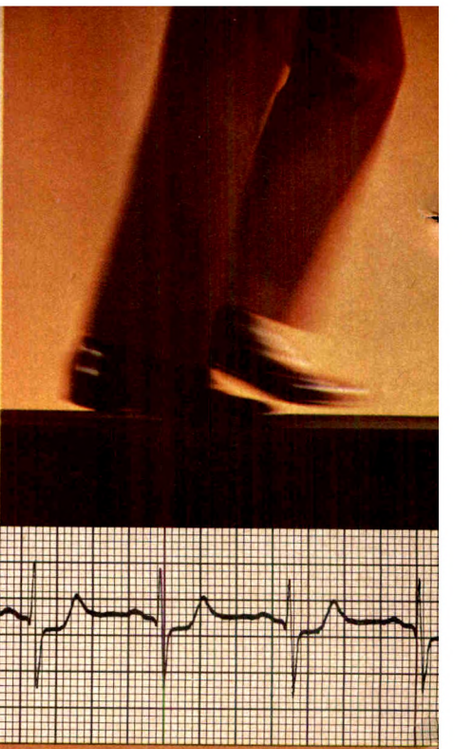

4th Minute at 3 mph (8th minute of test), 0% Grade, V-5, HR-83. (The patient's ECG indicates 1 mm of S-T depression.) Fully shielded cable and leadwire provide an effective barrier to the electrical interference that might otherwise mask small amounts of S-T depression.

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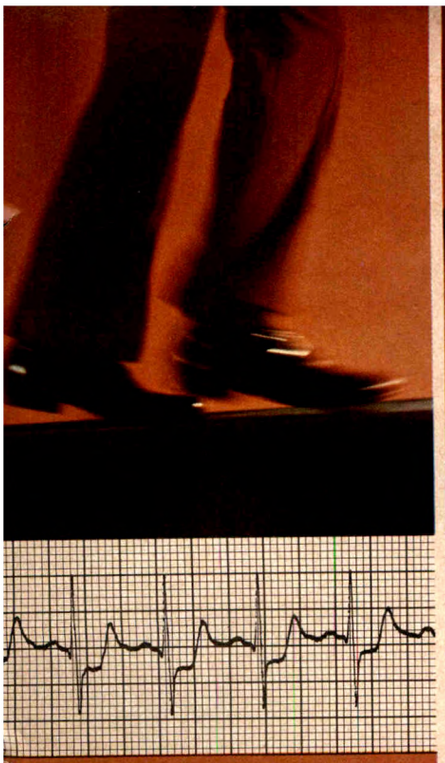
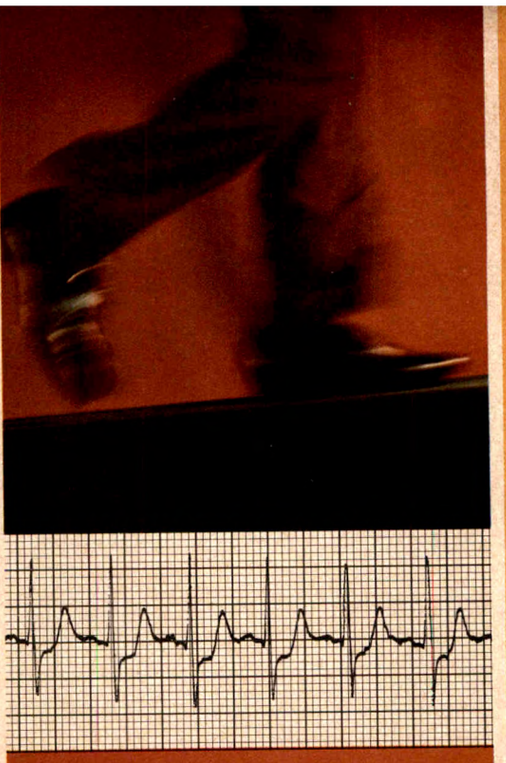


th Minute at 3 mph (12th minute f test), 5% Grade, V-5, HR-117. S-T depression increases to 2.5 mm.) Even at high work loads, the Ameri-an Stress Test Electrode and fully hielded cable system delivers a stable ase line and noise-free signal.



4th Minute at 3 mph (16th minute of test), 7.5% Grade, V-5, HR-135. (S-T depression drops to 2.0 mm.) Long test procedures seldom affect the electrode's contact with a patient's skin; trace quality remains high, even with patients who perspire heavily.

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Rheumatic Fever and Rheumatic Heart Disease	17
Hypertensive Heart Disease	7
Ischemic Heart Disease	15
Diseases of the Pericardium, Endocardium, and Myocardium	16
Cardiovascular Diseases	6
Arterial Diseases	10
Pulmonary Embolism with Infarction	125
Other Venous Emboli and Thrombi	87
Lower Extremity Varicosities	30
Other Lymphatic Diseases	8
Other Circulatory Diseases	8

These Patients Deserve Additional Protection Against Thromboembolic Disease...

*"Basic data for use in this study were supplied by the Commission on Professional and Hospital Activities (CPHA), Ann Arbor, Michigan. In these data the identities of individual hospitals were not revealed in any way. Although statistical testing was done at CPHA, any analysis, interpretation, or conclusions based on the data is solely that of the Kendall Corporation and CPHA specifically disclaims responsibility for any such analysis, interpretation, or conclusion."

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* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: Sublingual and chewable dosage forms of SORBITRATE are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

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162 Effect of Nitroglycerin Ointment on the Clinical and Hemodynamic Response to Exercise

JOHN O. PARKER, RAYMOND J. AUGUSTINE, JEFFREY R. BURTON, ROXROY O. WEST and PAUL W. ARMSTRONG

In 12 patients with coronary artery disease and exertional angina and in 8 patients with no or nonsignificant coronary arteriographic changes and no angina, nitroglycerin ointment significantly decreased left ventricular end-diastolic pressure and systemic arterial pressure within 15 minutes, the reduction lasting for at least 60 minutes. It also decreased cardiac, stroke, left ventricular stroke work and tension-time indexes. Exercise tolerance at this time was also improved. These results suggest that the beneficial effects of nitroglycerin ointment are related to a reduction in myocardial oxygen requirements.

167 Association of Ostium Secundum Atrial Septal Defects With Mitral Valve Prolapse

ROBERT D. LEACHMAN, DENNIS V. COKKINOS and DENTON A. COOLEY

Severe prolapse of the mitral valve leaflets was seen at left ventricular angiography in 17 percent of 92 patients over 35 years of age with a secundum type of atrial septal defect. Nine patients required angioplasty or mitral valve replacement. In a retrospective series of 122 surgical patients over age 15 years, mitral regurgitation due to prolapse was seen at operation in 9, and chordal rupture was seen at a later operation in 3. These findings indicate that the syndrome of mitral valve prolapse may be less benign than is commonly thought.

EXPERIMENTAL STUDIES

170 Ventricular Monophasic Action Potential Changes Associated With Neurogenic T Wave Abnormalities and Isoproterenol Administration in Dogs

CHIEN SUU KUO and BORYS SURAWICZ

Left stellate ganglion transection and right stellate ganglion stimulation both altered T wave polarity in the same direction in the dog ventricle; the former prolonged and the latter shortened the Q-T interval. Isoproterenol normalized the neurogenic T wave abnormalities caused by these procedures and shortened the previously prolonged monophasic action potential. The T wave was found to be a sensitive indicator of relatively small changes (less than 20 msec) in the sequence of ventricular repolarization.

178 Cardiac Dysrhythmias in the Conscious Dog After Surgically Induced Autonomic Imbalance

WALTER C. RANDALL, MICHAEL P. KAYE, GILBERT R. HAGEMAN, H. KURT JACOBS, DAVID E. EULER and WILLIAM WEHRMACHER

Exercise of trained unanesthetized dogs with total denervation of the heart except for the area supplied by the ventrolateral cardiac nerve with its sympathetic stimuli intact caused reproducible tachydysrhythmias including shifting cardiac pacemakers to low atrial or functional regions, supraventricular, atrioventricular junctional and ventricular tachycardias and frequent premature systoles. This animal model should be useful to demonstrate ways in which the autonomic nervous system may play a role in inducing cardiac dysrhythmias.

Continued on page A19

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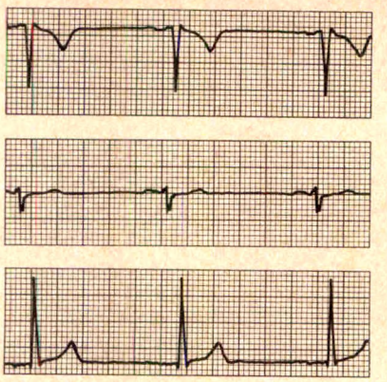

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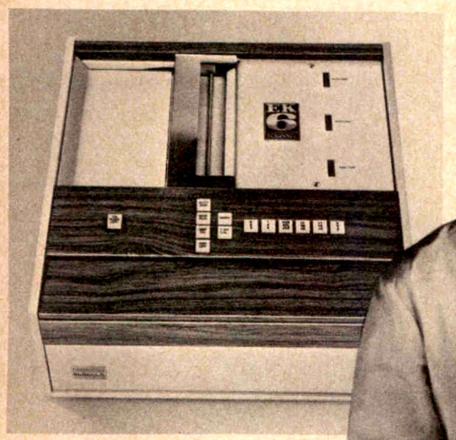

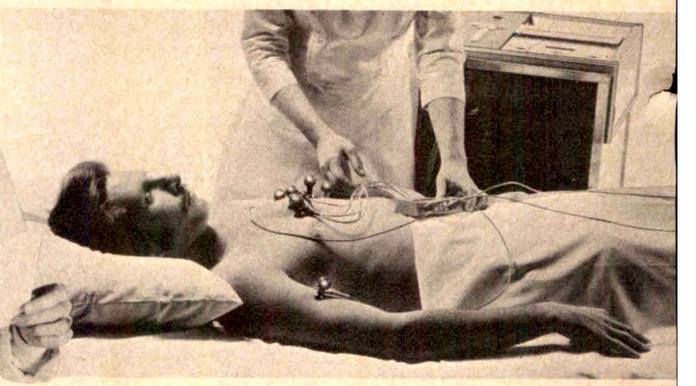

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184 **Effect of Nitroglycerin on Ventricular Fibrillation Threshold of Nonischemic Myocardium**

NEIL DASHKOFF, J-MICHEL A. ROLAND, P. JACOB VARGHESE and BERTRAM PITT

The electrophysiologic effects of intravenously administered nitroglycerin in raising the ventricular fibrillation threshold in 14 nonischemic open chest dogs from a mean control value of 24 ± 3 to 41 ± 6 milliamperes do not require the presence of myocardial ischemia and are independent of nitroglycerin's peripheral hemodynamic action or hypotensive effect. The precise mechanism by which nitroglycerin raises the ventricular fibrillation threshold remains uncertain, but it may be by a direct effect on the coronary circulation.

REPORTS ON THERAPY

189 **Effect of Amiodarone in the Wolff-Parkinson-White Syndrome**

HEIN J. J. WELLENS, K. I. LIE, FRITS W. BÄR, JAN C. WESDORP, HENK J. DOHMEN, DONALD R. DÜREN and DIRK DURRER

Amiodarone lengthened the effective refractory period of the accessory pathway in an atrioventricular direction in all 15 patients with the Wolff-Parkinson-White syndrome and in a ventriculoatrial direction in 8 of the same 15 patients. Circus movement tachycardia could no longer be initiated in 5 patients, and in the other 10 patients the rate of the tachycardia was slower than before treatment. This action makes the drug especially useful in patients with this syndrome and atrial fibrillation.

195 **Efficacy of Cardioselective Beta Adrenergic Blockade With Intravenously Administered Tolamolol in the Treatment of Cardiac Arrhythmias**

EZRA A. AMSTERDAM, GARRETT LEE, STEPHEN MORRISON, MELVIN J. TONKIN, ANTHONY N. DeMARIA and DEAN T. MASON

Tolamolol, a cardioselective beta adrenergic blocking agent, effectively controlled the ventricular rate in 85 percent of 19 patients with supraventricular arrhythmias, converted the arrhythmia to sinus rhythm in 2, and reduced the frequency of ventricular ectopic beats in 4 of 8 patients. The drug is particularly useful in patients with obstructive pulmonary disease who need cardiac beta adrenergic blockade. Hypotension is an important potential side effect.

200 **Patient-Initiated Rapid Atrial Pacing to Manage Supraventricular Tachycardia**

ALAN KAHN, JAMES J. MORRIS and PAUL CITRON

Patient-initiated rapid atrial pacing with use of an external transmitter and a permanent artificial pacemaker sutured to the right atrial myocardium successfully managed recurrent supraventricular tachycardia refractory to drug therapy in 10 of 12 patients for 15 to 36 months. Prescreening of patients with temporary rapid atrial pacing is required to verify the effectiveness of the technique and to exclude anomalous conduction pathways (preexcitation).

205 **Permanent Pacing in Patients With Transient Trifascicular Block During Acute Myocardial Infarction**

WILLIAM S. RITTER, JAMES M. ATKINS, C. GUNNAR BLOMQVIST and CHARLES B. MULLINS

Prophylactic permanent pacing significantly improved the long-term prognosis of patients who had right bundle branch block, left anterior hemiblock and transient complete heart block during acute myocardial infarction and survived to hospital discharge. Mean survival time was prolonged to 20 months compared with 2.4 months in a previously untreated and comparable group.

Continued on page A21

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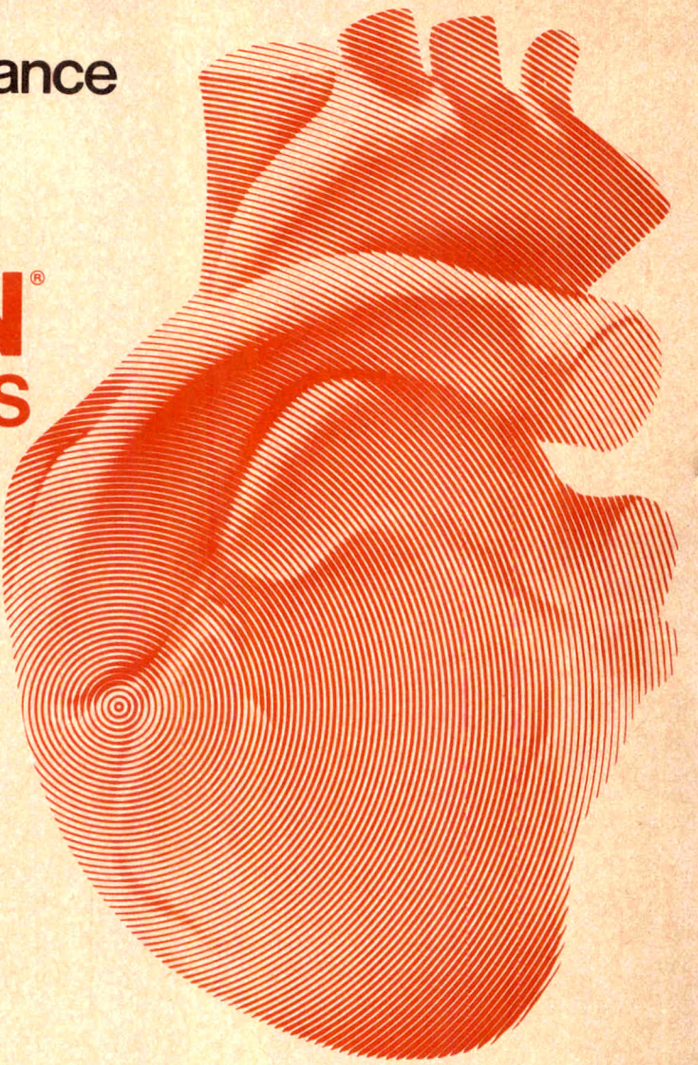

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*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

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PEDIATRIC CARDIOLOGY

209 Comparative Response of Right and Left Ventricles to Volume Overload

RAJAMMA MATHEW, OTTO G. THILENIUS and RENE A. ARCILLA

In both atrial septal defect and patent ductus arteriosus the ipsilateral (involved) ventricle had increased volume output and ejection fraction and increased distensibility. The contralateral (left) ventricle in atrial septal defect had a smaller than normal volume, output and ejection fraction; in patent ductus the contralateral (right) ventricle remained normal. These data in children suggest that left heart changes in atrial septal defect may be related to a functionally restrictive defect and to a difference in distensibility of the ventricles.

218 Fetal and Infant Death, Twinning and Cardiac Malformations in Families of 2,000 Children With and Without Cardiac Defects

RAY C. ANDERSON

The incidence of twinning in probands, siblings and parents of 2,000 children with a congenital cardiac malformation was the same as in the general population. The risk of recurrent cardiac malformations was 1.4 to 3 percent in families in which one child was born with a cardiac malformation of unknown origin, but there was no significant difference for the various malformations. The risk increases to 5 to 10 percent if a second case occurs in a sibship and to 10 to 20 percent if a parent is also affected.

225 Postoperative Pathology of Congenital Heart Disease

RICHARD VAN PRAAGH and MARC S. VISNER

This study of 2,365 autopsies performed at the Children's Hospital Medical Center in Boston from 1966 through 1974 reveals that 25 percent of patients had congenital heart disease. Tetralogy of Fallot and *d*-transposition of the great arteries, accounting for 25 and 15.5 percent of deaths, respectively, were the two conditions most frequently encountered in the postoperative series of 348 surgically treated subjects. Causes of late postoperative death included arrhythmias, excessively small ventricular septal defect with tricuspid atresia, massive hemoptysis, cyanotic spell, congestive heart failure and infection.

231 Long-Term Follow-Up of Valvulotomy for Congenital Aortic Stenosis

W. DAVID JACK, II and DAVID T. KELLY

This long-term (10.6 years) follow-up study of 42 patients subjected to valvulotomy for severe congenital aortic valve stenosis showed an annual mortality rate of 0.5 percent and amelioration of major symptoms in all patients, thus confirming the effectiveness and value of this palliative procedure. All such surgically treated patients should have cardiac catheterization within a year after operation and every 5 years thereafter, or sooner if clinical events warrant it, to determine the degree of restenosis and the need for reoperation and valve replacement. Valvulotomy remains the preferred surgical procedure in children and young adults.

Continued on page A23

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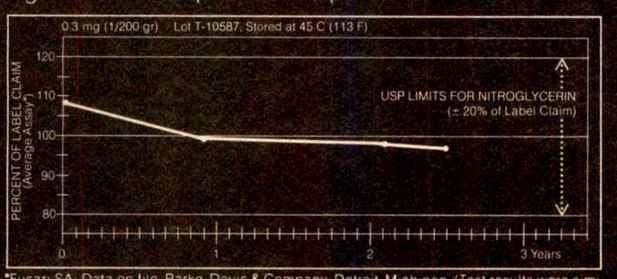

*Fusari SA: Data on file, Parke, Davis & Company, Detroit, Michigan. (Test results were similar for the 0.4-mg and the 0.6-mg strengths.)

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235 Tricuspid Atresia: Results of Treatment in 160 Children

WILLIAM G. WILLIAMS, LORRAINE RUBIS, RODNEY S. FOWLER, MINOO K. RAO, GEORGE A. TRUSLER and WILLIAM T. MUSTARD

Classifying and treating children with tricuspid atresia according to total pulmonary blood flow simplifies their clinical management. The majority of children require operative treatment in the first year of life. For those with decreased pulmonary flow, a Potts shunt followed later by a Glenn anastomosis or possibly the Fontan procedure is recommended; for children with increased pulmonary blood flow and transposition of the great arteries, pulmonary arterial banding in infancy appears the most appropriate technique for controlling congestive failure and preventing pulmonary vascular disease.

241 Cardiac Rhabdomyoma: A Clinicopathologic and Electron Microscopic Study

JOHN J. FENOGLIO, Jr, HUGH A. McALLISTER, Jr and VICTOR J. FERRANS

Cardiac rhabdomyomas are rare tumors of infancy that derive from cardiac muscle cells and represent hamartomas rather than true tumors. In this series of 36 patients, 78 percent were under 1 year of age and only 1 patient was over 15 years of age. Most tumors were multiple and involved with equal frequency the right and left ventricles; 30 percent involved the atria. Histologically they were composed of classic "spider cells." Obstruction of intracardiac blood flow was present in half the patients and accounted for the clinical symptoms in nine patients.

CASE REPORTS

252 Atrial Myxoma in a Family

PENTTI SILTANEN, LEENA TUUTERI, REIJO NORIO, PEKKA TALA, PIA AHRENBERG and PENTTI I. HALONEN

The occurrence of atrial myxoma in a mother and three of her seven children suggests a dominant familial transmission of this condition. The myxomas were successfully removed in the three children, but the mother, who had biatrial myxoma, died from massive intraoperative embolization.

257 Surgical Treatment of Congenital Unilateral Pulmonary Arterial Stenosis With Contralateral Pulmonary Hypertension

LAWRENCE H. COHN, JOHN H. SANDERS, Jr and JOHN J. COLLINS, Jr

A bypass graft from the main pulmonary artery to the distal right pulmonary artery immediately reduced by 50 percent the mean left pulmonary arterial pressure and progressively improved the clinical condition of this 48 year old woman with congenital right pulmonary arterial ostial stenosis and systemic levels of pressure in the main left pulmonary artery.

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261 **Masked Abnormal Drainage of the Inferior Vena Cava Into the Left Atrium**

AMARJIT SINGH, EUGENIE F. DOYLE, DELORES DANILOWICZ and FRANK C. SPENCER

Persistent cyanosis following closure of a large atrial septal defect in a 2 year old child eventually led to a repeat study that revealed direct drainage of the inferior vena cava into the left atrium with moderate arterial oxygen desaturation. At the age of 6, the child underwent a second open heart procedure that identified and successfully corrected the unusual anomaly.

265 **Aneurysm of the Atrial Septum in Tricuspid Atresia. Diagnosis During Life and Therapy**

ROBERT M. FREEDOM and RICHARD D. ROWE

Satisfactory decompression was achieved by a Blalock-Hanlon atrial septectomy and a Waterston shunt in this 3 day old infant with tricuspid atresia and massive aneurysmal dilatation of the foramen ovale. Unfortunately the infant died 3 days later from sepsis.

EDITORIALS

268 **Diagnostic Considerations in Electromechanical Dissociation**

HOWARD S. FRIEDMAN

SPECIAL DEPARTMENTS

271 **Letters to the Editor**

Mitral Valve Prolapse-Click Syndrome—I and II
McCormick, Hurst and Jeresaty

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275 **American College of Cardiology News**

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Calendar of Continuing Education Programs

CORRECTION

An erroneous statement was made in the article on "High Blood Pressure in Children: Problems and Guidelines for Evaluation and Treatment" in the March 31 issue of the Journal (Londe S, Goldring D: Am J Cardiol 37:650–657, 1976). Sentence 4 in the section on plasma renin activity on 656 should read, "Normotensive subjects responded with an increase in renin."

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CONTRAINDICATIONS It should not be used in the treatment of compensatory hypertension, such as that associated with aortic coarctation or arteriovenous shunt, nor in patients hypersensitive to diazoxide or other thiazides, unless the potential benefits outweigh the possible risks.

WARNINGS Safety in pregnancy and in children has not yet been established. Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults. Hypotension may occasionally result. If severe enough to require therapy, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine. Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored, especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide. Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. Concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions). Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent. Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

PRECAUTIONS HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available. It should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively. Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response. As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental. Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection. Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

ADVERSE REACTIONS

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by unconsciousness, convulsions, paralysis, confusion or focal neurological deficit, such as numbness of the hands; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions, such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported. Papilledema, induced by plasma volume expansion secondary to the administration of diazoxide, was reported in one patient who had received eleven injections over a twenty-two day period.

Other adverse reactions: Vasodilative phenomena, such as orthostatic hypotension, sweating, flushing, and generalized or localized sensations of warmth; supraventricular tachycardia and palpitation; bradycardia; various transient neurological findings secondary to alterations in regional blood flow to the brain, such as headache (sometimes throbbing), dizziness, lightheadedness, sleepiness (also reported as lethargy, somnolence or drowsiness), euphoria or "funny feeling", ringing in the ears and momentary hearing loss, and weakness of short duration; chest discomfort or nonanginal "tightness in the chest"; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; and various respiratory and gastrointestinal findings, secondary to the relaxation of smooth muscle, such as dyspnea, cough and choking sensation; nausea and vomiting and/or abdominal discomfort, anorexia, alteration in taste, parotid swelling, salivation, dry mouth, lacrimation, ileus, constipation and diarrhea. Also, warmth or pain along the injected vein; cellulitus without sloughing and/or phlebitis at the site of extravasation; back pain; and increased nocturia. Apprehension or anxiety, malaise and blurred vision occurred on single occasions.

DRUG INTERACTIONS Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

OVERDOSAGE Overdosage may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agent suggests that the hypotension may have been caused by something other than diazoxide. Excessive hypergiycemia resulting from overdosage will respond to conventional therapy of hyperglycemia. Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

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direct-action

Hyperstat® I.V.

Brand of DIAZOXIDE

INJECTION
20 ml ampule
contains 300 mg

"The injection of the [diazoxide] bolus in 10 to 15 seconds results in a prompt blood pressure fall in a high percentage of cases. A maximal blood pressure response usually occurs within 5 to 10 minutes."*

☐ Rapid reduction to normotensive levels

Induces rapid reduction of blood pressure generally within 5 minutes...often in 1 or 2 minutes to the lowest level achieved. Blood pressure response facilitated by appropriate diuretic therapy.

☐ Prolonged activity

A single injection of HYPERSTAT I.V. generally maintains blood pressure below pretreatment levels for periods up to 12 hours.

☐ Protective action—helps avert target organ damage

Cardiac output increases as diastolic pressure is reduced. Coronary and cerebral blood flow maintained. Increased renal blood flow after transient decrease.

☐ Uncomplicated procedure

Simple I.V. "push" in a peripheral vein in 30 seconds or less. Close monitoring at frequent intervals is necessary until blood pressure is stabilized (generally 15-30 minutes). Thereafter, hourly measurement should be taken during the balance of effect.

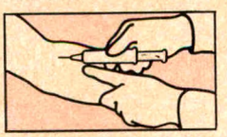
☐ Convenient...no preparation

HYPERSTAT I.V. supplied as a 20 ml ampule containing 300 mg diazoxide in ready to use solution.

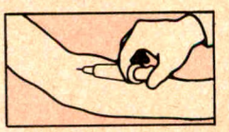
*Marvin Moser, M.D., Assistant Professor of Clinical Medicine, Albert Einstein College of Medicine, and Chief of Cardiology, White Plains Hospital, White Plains, N.Y., in Diazoxide—an effective vasodilator in accelerated hypertension. *Am Heart J* 87(6): 791-795, June 1974.

Administration guidelines

1. Fill dry syringe with appropriate dose of HYPERSTAT I.V. Injection (20 ml ampule contains 300 mg diazoxide).



2. Hospitalized patient should be recumbent. Insert needle only into a peripheral vein.



3. Inject entire dose I.V. in 30 seconds or less. Remove needle carefully—avoid extravasation.

4. Keep patient recumbent for at least half an hour after injection; monitor BP closely until stabilized—usually 15-30 minutes.

5. If patient is to be ambulatory, measure BP in standing position before ending surveillance.

6. HYPERSTAT I.V. Injection should be continued until a regimen of oral antihypertensive medication becomes effective (generally within a few days).

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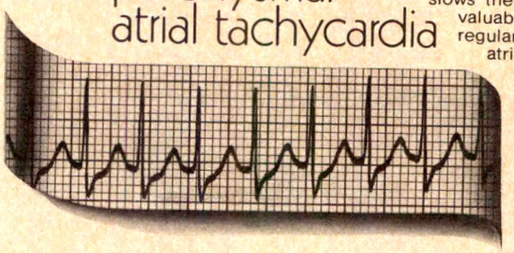
Before prescribing HYPERSTAT I.V. Injection, please consult complete product information, a summary of which appears on the facing page.

in the inner circle of Inderal® stands out

The place of INDERAL (propranolol hydrochloride) among the standard drugs for the treatment of disturbed cardiac rhythm has been frequently reaffirmed throughout eight years of clinical use. In fact, after withdrawal of digitalis, "...it may be the treatment of choice for digitalis-induced arrhythmias, provided hypokalemia is not present."[1] It has been widely used in selected supraventricular arrhythmias that have proved resistant to digitalis and in tachyarrhythmias precipitated by exercise, emotional stress, or undesirable sympathetic stimulation; and it is also effective in controlling supraventricular tachyarrhythmias related to the Wolff-Parkinson-White syndrome.[2]

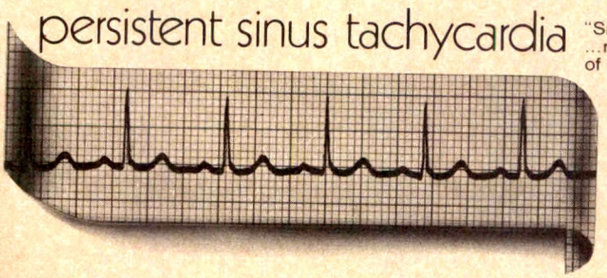
INDERAL protects the heart from undesirable catecholamine stimulation through its beta blocking action. Propranolol occupies the beta-receptor sites, making them unavailable to the beta-adrenergic stimulating effects of catecholamines. INDERAL is the first beta-adrenergic blocking agent in clinical cardiologic use.

paroxysmal atrial tachycardia



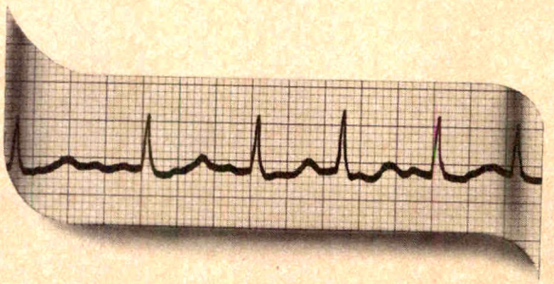
"In paroxysmal atrial tachycardia, the drug slows the ventricular rate, and also is valuable in restoring the heart to a regular sinus rhythm."[3] "Paroxysmal atrial tachycardia induced by exercise...has uniformly been prevented by propranolol," and results with INDERAL in the Wolff-Parkinson-White syndrome"...have been favorable in all but a few patients reported. This condition appears to be one of the more definite indications for propranolol."[4]

persistent sinus tachycardia



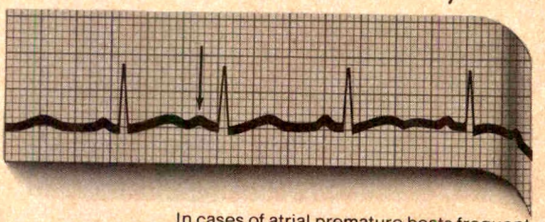
"Sinus tachycardia induced by stress ...may be inappropriate to the needs of the patient and, in fact, may be causing symptoms of itself. If the clinical situation does not suggest a needed compensatory sinus tachycardia and the heart rate is indeed inappropriate, treatment with propranolol has been successful."[4]

tachycardias and arrhythmias due to thyrotoxicosis



Although propranolol may accomplish only the reduction of the heart rate in hyperthyroidism, it has proved useful for this purpose. "Sinus tachycardia in hyperthyroidism which causes symptoms may be relieved by the administration of propranolol before definitive therapy....The author has observed that atrial fibrillation complicating hyperthyroidism was easily terminated using modest doses of propranolol."[4]

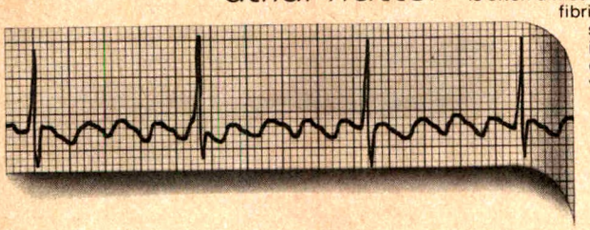
persistent atrial extrasystoles



In cases of atrial premature beats frequent enough that they could herald the onset of atrial fibrillation, it has been recommended that propranolol be used after other measures have failed to control the beats.[5]

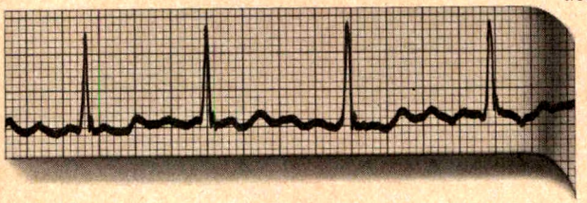
ntiarrhythmia agents
or supraventricular arrhythmias

atrial flutter



"In the presence of atrial flutter, ventricular rate is often difficult to control, and, as with an atrial fibrillation, propranolol hydrochloride should be added when the flutter is not controlled by digitalis, especially in the presence of mitral valve disease."[6]

atrial fibrillation



"One salutary effect of propranolol is slowing of the ventricular rate in atrial flutter and fibrillation."[4] In a review of the literature, it was noted that most patients with fibrillation not controlled by digitalis alone experienced slowing of the ventricular rate after administration of propranolol and a few reverted to sinus rhythm.[7]

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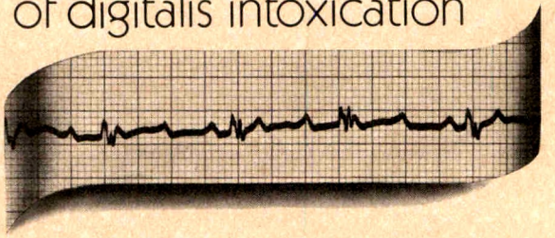
and for tachyarrhythmias of digitalis intoxication

"Propranolol is very effective in treating arrhythmias caused by digitalis excess. Its use in this setting may be limited by the presence of significant congestive heart failure or heart block, both of which can be potentiated by propranolol. However, if given in small doses with careful monitoring, it is often of great value in the treatment of digitalis toxicity."[5]



References 1. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 2. Chung, E.K.: Postgrad. Med. *53*:107 (Apr.) 1973. 3. Harrison, D.C.: Clinical Guide to the Use of Beta-Adrenergic Blockade in Arrhythmias, Ayerst Laboratories, 1971, p. 10. 4. Reynolds, E.W.: Geriatrics *26*:150 (Feb.) 1971. 5. Helfant, R.H.: Med. Times *98*:118 (Jan.) 1970. 6. Sonnenblick, E.H.: Arrhythmias and Beta-Adrenergic Blockade, Ayerst Laboratories, 1971, p. 7. 7. Gibson, D., and Sowton, E.: Prog. Cardiovasc. Dis. *12*:16 (July) 1969.

Inderal®

Brand of propranolol hydrochloride

Tablets 10mg., 40mg., 80mg.

helps prevent or control catecholamine-induced cardiac arrhythmias

Ayerst

AYERST LABORATORIES
New York, N.Y. 10017

BETA-BLOCKADE/**INDERAL**®
(propranolol hydrochloride)

(See last page of advertisement for prescribing information.)

BRIEF SUMMARY
(For full prescribing information, see package circular.)

Inderal®

Brand of
propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support or vital functional balances.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS

Cardiac Arrhythmias

1.) Supraventricular arrhythmias
   a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)
   b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.
   c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.
   May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)
   d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.
   e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias
   Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.
   a) Ventricular tachycardias
   With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*
   b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication
   If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)
   Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia
   Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis

INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma

After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). However, the inotropic action of digitalis may be reduced by INDERAL'S opposite inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues, INDERAL therapy must be immediately withdrawn; (b) if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH CORONARY ARTERY DISEASE AND/OR ANGINA PECTORIS, when discontinuance of chronically administered INDERAL is planned, the dosage should be gradually reduced over a period of several weeks and the patient should continue to be carefully monitored. There have been reports of exacerbation of angina and myocardial infarction occurring following *abrupt* discontinuation of INDERAL therapy.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of continuing hyperthyroidism or complications and give a false impression of improvement. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg. propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta-blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. Especially important with labile diabetics.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The oral route of administration is preferred.

ORAL

ARRHYTHMIAS—10-30 mg. three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg. three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg. daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic-blocking agent.

—*Management of inoperable tumor*—30 mg. daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg. administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg. (1 cc.) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED: BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg.): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED: INDERAL (propranolol hydrochloride) TABLETS

No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each tablet contains 80 mg. of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

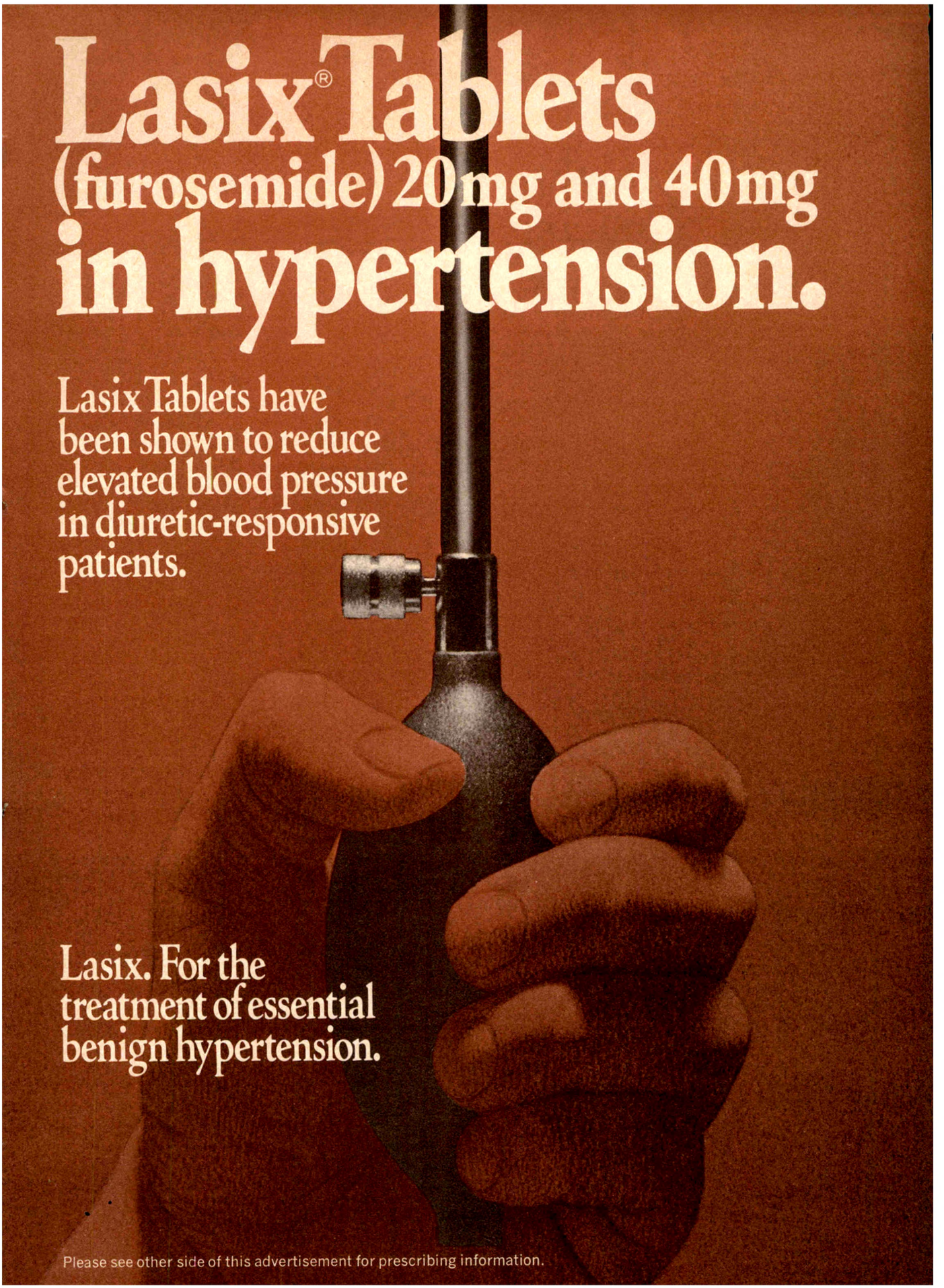
No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls in boxes of 10.

7613

Ayerst®
AYERST LABORATORIES
New York, N.Y. 10017

Lasix® Tablets (furosemide) 20 mg and 40 mg in hypertension.

Lasix Tablets have been shown to reduce elevated blood pressure in diuretic-responsive patients.



Lasix. For the treatment of essential benign hypertension.

Please see other side of this advertisement for prescribing information.

Lasix® Tablets (furosemide) 20 mg and 40 mg in hypertension.

A brief summary of the Prescribing Information for

Lasix® (furosemide) Tablets 20 mg and 40 mg

WARNING—Lasix (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Indications—Lasix (furosemide) is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.

Hypertension—Lasix (furosemide) may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix (furosemide) alone.

CONTRAINDICATIONS—Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. (See "Additional Information.")

Lasix (furosemide) is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with a history of hypersensitivity to this compound.

Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

Patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, an oral liquid preparation should be used rather than enteric-coated potassium salts.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix (furosemide).

Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

When parenteral use of Lasix (furosemide) precedes its oral use, it should be kept in mind that cases of tinnitus and reversible hearing impairment have been reported. There have also been some reports of cases in which irreversible hearing impairment occurred. Usually, ototoxicity has been reported when Lasix (furosemide) was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were often given. If the physician elects to use high dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable (for adults, it has been reported that an infusion rate not exceeding 4 mg Lasix [furosemide] per minute has been used).

Increases in blood glucose, and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix (furosemide) may lower serum calcium levels, and rare cases of tetany have been reported.

Patients receiving high doses of salicylates, in conjunction with Lasix (furosemide) may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, Lasix (furosemide) and cephaloridine should not be administered simultaneously.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue Lasix (furosemide) for one week prior to any elective surgery.

Adverse Reactions—Various forms of dermatitis, including urticaria and rare forms of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura). Rare cases of agranulocytosis which responded to treatment.

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli and acute pancreatitis.

Lasix (furosemide)-induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

Dosage and Administration

ADULTS

The usual adult dose of Lasix (furosemide) is 20 to 80 mg given as a single dose.

If the diuretic response with a single dose of 20 to 80 mg is not satisfactory, the following schedule should be used: Increase this dose by increments of 20 or 40 mg not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. The dose of Lasix (furosemide) may be carefully titrated up to 600 mg per day in those patients with severe clinical edematous states.

With doses exceeding 80 mg/day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension—The usual dose of Lasix (furosemide) is 40 mg twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50 percent as soon as Lasix (furosemide) is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix (furosemide), a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if 40 mg twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents, e.g., reserpine, rather than to increase the dose of Lasix (furosemide).

INFANTS AND CHILDREN

Pediatric Administration: The usual initial dose of oral Lasix in infants and children is 2 mg/kg body weight, given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg not sooner than 6 to 8 hours after the previous dose. Doses greater than 6 mg/kg body weight are not recommended.

For maintenance therapy in infants and children, the dose should be adjusted to the minimum effective level.

How Supplied—Lasix Tablets 40 mg (furosemide) supplied as white, round, monogrammed, scored tablets.

Lasix Tablets 20 mg (furosemide) supplied as white, oval, monogrammed tablets.

Note: Dispense in dark containers. Exposure to light may cause slight discoloration which, however, does not alter potency.

Additional Information

Toxicology

The acute toxicity of Lasix (furosemide) has been determined in mice, rats, and dogs. In all three animal species, the oral LD_{50} of Lasix (furosemide) exceeded 1000 mg/kg of body weight, while the intravenous LD_{50} ranged from 300 to 680 mg/kg. Intragastric injection of the drug in newborn rats resulted in an LD_{50} of 380 mg/kg.

The acute toxicity of high doses of Lasix (furosemide) was characterized by convulsions, paralysis, and collapse. Surviving animals often became dehydrated and depleted of electrolytes due to the diuresis induced by Lasix (furosemide). In the newborn rats, intragastric injection of the drug caused hyperactivity and anorexia.

Chronic toxicity studies with Lasix (furosemide) were done in rats and dogs. In a one-year study in rats, renal tubular degeneration occurred, with all doses higher than 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day). A six-month study in dogs revealed calcification and scarring of the renal parenchyma at all doses above 10 mg/kg (83 percent of the maximal recommended human dose of 600 mg per day).

Reproductive Studies

The effects of Lasix (furosemide) on embryonic and fetal development and on pregnant dams were studied in mice, rats, and rabbits.

Lasix (furosemide) caused unexplained maternal deaths and abortions in the rabbit when 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day) was administered between days 12 to 17 of gestation. In a previous study the lowest dose of only 25 mg/kg (2 times the maximal recommended human dose of 600 mg per day) caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality which can precede maternal deaths.

The results of the mouse study and one of the three rabbit studies also showed an increased incidence of hydronephrosis (distention of the renal pelvis and, in some cases, of the ureters) in fetuses derived from treated dams as compared to the incidence in fetuses from the control group.

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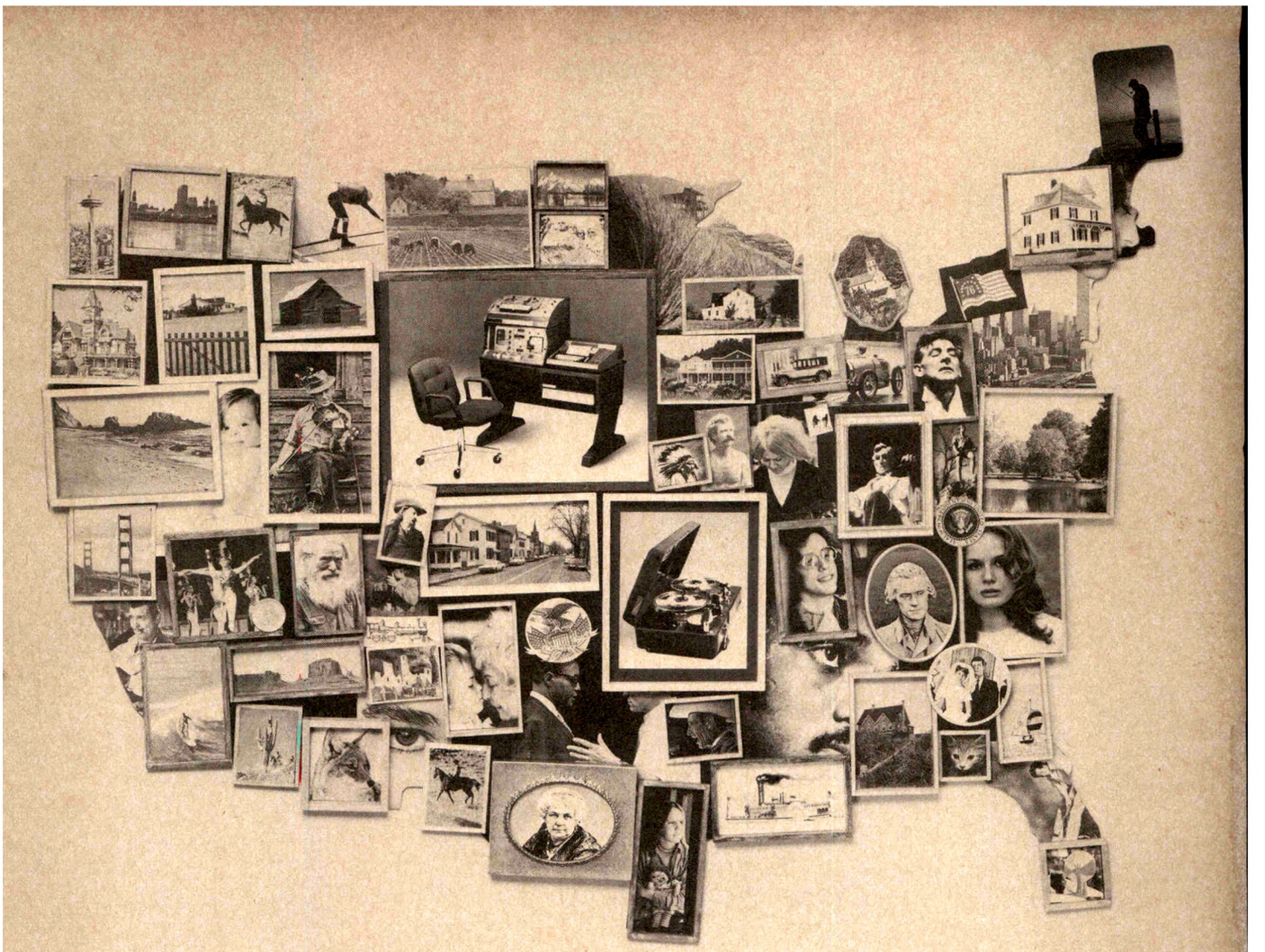

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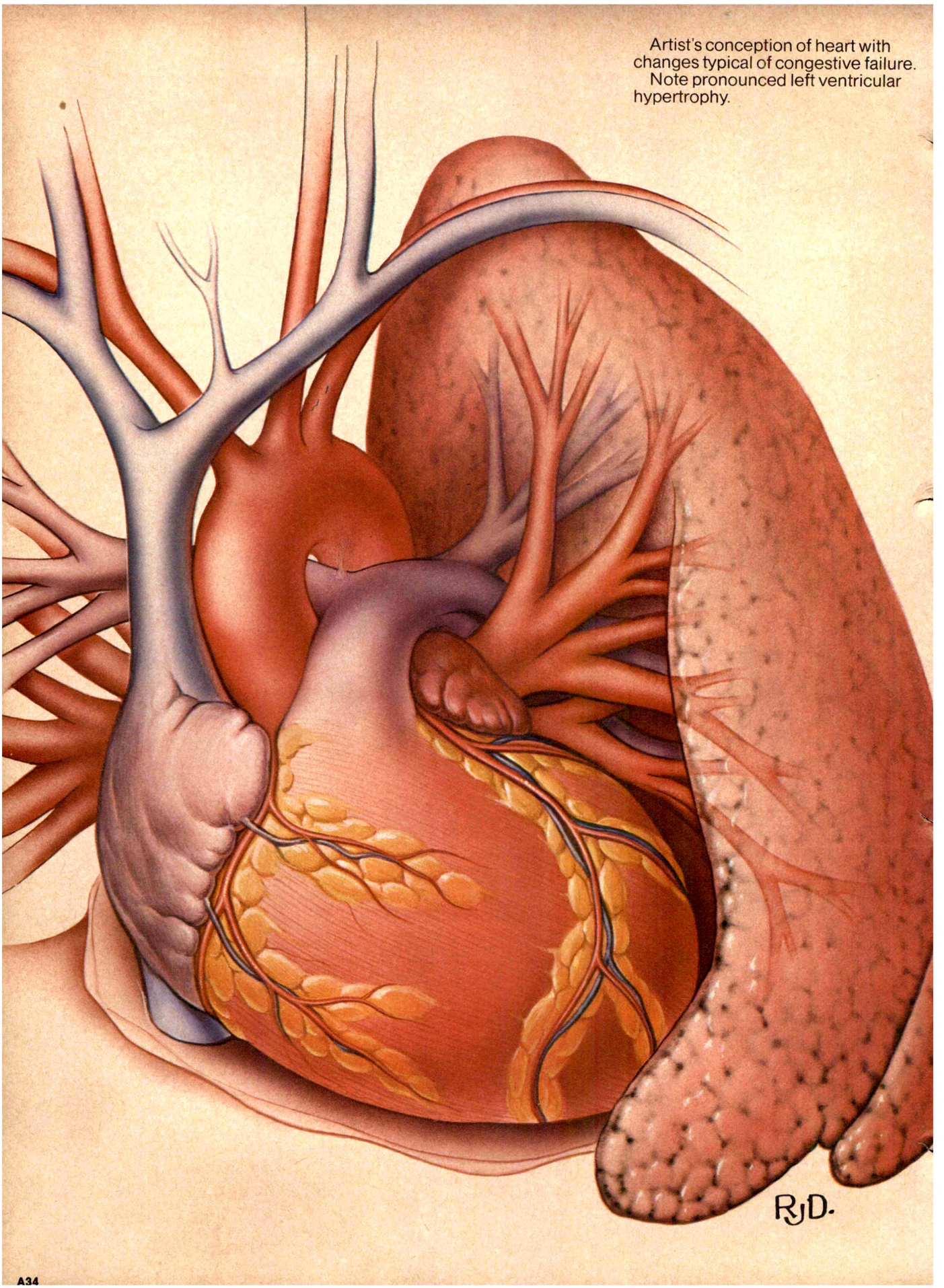

Artist's conception of heart with changes typical of congestive failure. Note pronounced left ventricular hypertrophy.

In congestive heart failure...

aldosteronism promotes edema. "The hyperaldosteronism present in the majority of patients with congestive heart failure...explains the low sodium excretion in urine, sweat, and saliva. Ultimately, of course, this retention of salt and water leads to edema."[1]

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In congestive heart failure

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Contraindications—Acute renal insufficiency, rapidly progressing impairment of renal function, anuria and hyperkalemia.

Warnings—Potassium supplementation may cause hyperkalemia and is not indicated unless a glucocorticoid is also given. Discontinue potassium supplementation if hyperkalemia develops. **Usage of any drug in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the mother and fetus.**

In a 78-week chronic toxicity study, rats were given daily oral doses of spironolactone approximately 30, 90 and 300 times the usual daily human therapeutic dose (100 mg. per day). The results of this study demonstrated a dose-related, statistically significant increase in the occurrence of benign adenomas of the testes and thyroid gland. Similar findings have not been demonstrated in other animal studies. In view of the marked differences in spironolactone metabolism by the rat and by man, the relationship of this finding to the possible development of tumors in humans is unknown.

Precautions—Patients should be checked carefully since electrolyte imbalance may occur. Although usually insignificant, hyperkalemia may be serious when renal impairment exists; deaths have occurred. Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, together with a low serum sodium may be caused or aggravated, especially when Aldactone is combined with other diuretics. Elevation of BUN may occur, especially with preexisting renal impairment. Mild acidosis may occur. Reduce the dosage of other antihypertensive drugs, particularly the ganglionic blocking agents, by at least 50 percent when adding Aldactone since it potentiates their action. The physician should be alert to the possible onset of gynecomastia.

Adverse Reactions—Drowsiness, lethargy, headache, diarrhea and other gastrointestinal symptoms, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, gynecomastia, inability to achieve or maintain erection, androgenic effects, including hirsutism, irregular menses and deepening voice. Adverse reactions are usually reversible. In rare instances gynecomastia may persist.

Dosage and Administration—For essential hypertension in adults the initial daily dosage is 50 to 100 mg. in divided doses. Aldactone may be combined with a thiazide diuretic if necessary. Continue treatment for two weeks or longer since the maximal response may not occur sooner. Adjust subsequent dosage according to response of patient.

For edema in adults initial daily dosage is 100 mg. in divided doses. Continue medication for at least five days to determine diuretic response; add a thiazide or organic mercurial if adequate diuretic response has not occurred. Aldactone dosage should not be changed when other therapy is added. A daily dosage of Aldactone considerably greater than 75 mg. may be given if necessary.

A glucocorticoid, such as 15 to 20 mg. of prednisone daily, may be desirable for patients with extremely resistant edema which does not respond adequately to Aldactone and a conventional diuretic. Observe the usual precautions applicable to glucocorticoid therapy; supplemental potassium will often be necessary. Such patients frequently have an associated hyponatremia—restriction of fluid intake to 1 liter per day or administration of mannitol or urea may be required (these measures are contraindicated in patients with uremia or severely impaired renal function). Mannitol is contraindicated in patients with congestive heart failure, and urea is contraindicated with a history or signs of hepatic coma unless the patient is receiving antibiotics orally to "sterilize" the gastrointestinal tract.

Glucocorticoids should usually be given first to patients with nephrosis since Aldactone, although useful for diuresis, will not directly affect the basic pathologic process.

For children the daily dosage should provide 1.5 mg. of Aldactone per pound of body weight.

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1. Genest, J., and Nowar, T.: Clinician: Congestive Heart Failure, Medcom* Learning Systems, New York, Medical Communications, Inc., 1972, pp. 42-49.
2. Laragh, J. H.: Hosp. Pract. 5:43-50 (Nov.) 1970.

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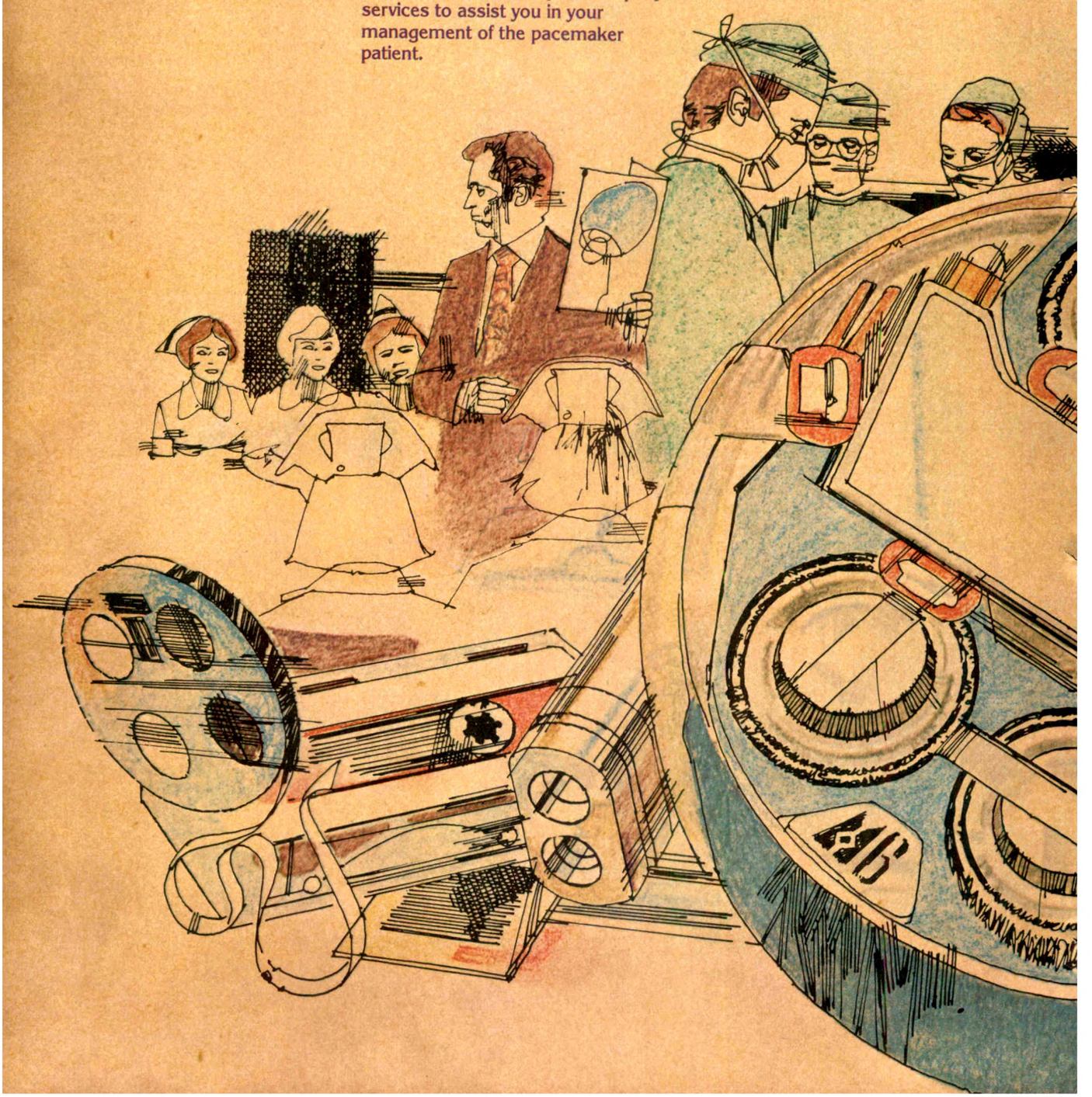

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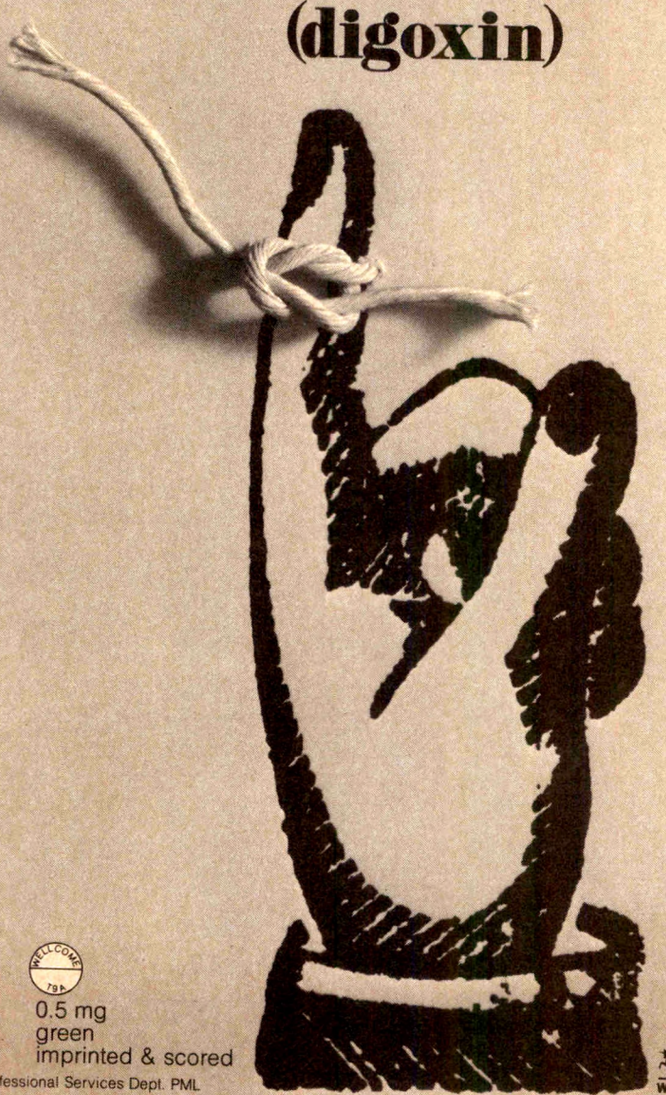

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NUMBER 2

CLINICAL STUDIES

Frequent or Complex Ventricular Ectopy in Apparently Healthy Subjects

A Clinical Study of 25 Cases

HAROLD L. KENNEDY, MD
STEPHEN J. UNDERHILL

Baltimore, Maryland

During 18 months, 25 asymptomatic apparently healthy subjects were consecutively studied because of electrocardiographic discovery of frequent (more than 3 beats/min) or complex (multiform, alternating or repetitive patterns) ventricular ectopy of unknown cause. History, physical examination, laboratory data, chest roentgenogram, vectorcardiogram, exercise testing, echocardiogram, His bundle electrogram and cardiac catheterization procedures were performed to detect cardiac abnormalities. Ventricular ectopy was studied with maximal exercise testing, 24 hour Holter recordings and antiarrhythmic drug regimens.

The duration of ventricular ectopy ranged from 1 to 30 years (mean 6). Eighteen subjects had an apparently normal cardiac status, and seven had mild or suspected abnormalities. Ventricular ectopy was of predominantly right ventricular origin in 19 of 25 subjects, and disappeared during maximal exercise in 21 of 23 subjects. Characteristic frequent (mean 559 beats/hour) and complex (bigeminal, trigeminal or ventricular couplet) ectopic beats were consistently present in all subjects during a 24 hour diurnal cycle. Antiarrhythmic drug regimens were generally ineffective.

Our data suggest that a clinical syndrome of frequent complex ventricular ectopy can occur in apparently healthy subjects. The etiology and natural history of this syndrome are undefined.

From the Department of Cardiovascular Service and Clinical Investigation, U. S. Public Health Service Hospital, and the Department of Social and Preventive Medicine, University of Maryland, Baltimore, Md. Manuscript received October 1, 1975; revised manuscript received January 9, 1976, accepted January 14, 1976.

Address for reprints: Harold L. Kennedy, MD, Department of Cardiovascular Service and Clinical Investigation, U. S. Public Health Service Hospital, 3100 Wyman Park Dr., Baltimore, Md. 21211.

Ventricular ectopic beats commonly occur in apparently healthy persons.[1,2] Although frequent or complex* ventricular ectopy is reported to be rare in such persons, its occurrence has been documented by electrocardiogram,[1,4,5] exercise testing[6–8] and Holter monitoring.[2,3,9] The clinical characteristics and natural history of persons with this finding

* Complex ventricular ectopy is defined in this report as multiform, alternating (bigeminy, trigeminy or quadrigeminy) or continuously repetitive (ventricular couplets or ventricular tachycardia) patterns.

are incompletely defined, but recent epidemiologic surveys[3,10,11] have focused attention on ventricular ectopy as a factor associated with increased long-term risk of death, including sudden death, although some controversy exists as to whether it is an independent factor. Thus, studies of ventricular ectopy in apparently normal persons seem warranted.

This report describes the evaluation and characteristics of 25 apparently healthy subjects discovered to have asymptomatic frequent and complex ventricular ectopic beats of unknown origin. It also examines the characteristics, types and frequency of these beats.

Methods

Subjects Studied

Twenty-five asymptomatic subjects were referred to us for cardiologic evaluation because ventricular ectopic beats that were frequent or complex, or both, were detected in the standard electrocardiogram as a result of accidental or circumstantial discovery or routine examination. Thirteen subjects represented 2 percent (13 of 632) of a cardiology referral practice from a community of 50,000 persons during a 12 month period. The remaining 12 subjects represented less than 1 percent (12 of 5,086) of beneficiaries of the U. S. Public Health Service Hospital of Baltimore, Md. (6 month census: 42,000 outpatients and 6,500 inpatients) referred to the Department of Cardiovascular Services during a 6 month period.

Clinical Evaluation

All subjects underwent a complete medical history and physical examination, and an effort was made to obtain old electrocardiograms and medical records. Standard hematologic, biochemical and urinary tests, fasting lipid studies, chest roentgenograms and follow-up electrocardiograms were also performed. Additional studies to examine the apparent health status of subjects varied according to availability of techniques or indications. Thus, Frank lead vectorcardiograms (10 subjects) and echocardiograms (11 subjects) were available only for the U. S. Public Health Service population. Likewise, electrocardiographic anomalous beat configurations of questionable origin provided an indication for His bundle electrographic study in five subjects, and the development of atypical chest pain in two subjects resulted in cardiac catheterization with coronary arteriography.

Evaluation of Ventricular Ectopy

Exercise testing procedure: After the clinical examination, a resting supine 12 lead electrocardiogram was obtained from all subjects before exercise testing. No subject exhibited abnormal Q or QS waves or recent S-T segment or T wave changes despite the presence of multiple ventricular ectopic beats. The exercise treadmill procedure was performed according to the method of Bruce.[12] The exercise test data were displayed on an oscilloscopic monitor, inscribed on a chart recorder and transcribed on magnetic tape for analysis and permanent storage. In addition to the standard exercise test observations, ventricular ectopy was graded during a 3 minute control period before exercise and during and 10 minutes after exercise. The system of Jelinek and Lown[13] was used to grade ventricular ectopic beats during exercise.

Holter recording procedure: Continuous 24 hour electrocardiographic recordings were obtained using a two channel model 425 Avionics Holter recorder (Avionics Biomedical Division, Del-Mar Engineering, Irvine, Calif.) driven by a hysteresis synchronous drive motor at a tape speed of approximately 7.5 inches (19.05 cm)/min with a frequency response of 0.07 to 100 hertz. Patients were connected to the recording apparatus 24 hours before exercise testing with standard nondisposable silver-silver chloride electrodes utilizing modified chest lead V_1[14] and chest bipolar lead V_5. This recorder was attached to a belt or shoulder harness and usually did not interfere with daily activity or exercise. During the recording period patients kept a chronologic diary of all physical, physiologic and emotional events (particularly noting hours of sleep).

Analysis of the recordings was accomplished with the model 660 Avionics Electrocardioscanner, which allowed playback of Holter tapes at a speed of 1, 30, 60 or 120 times real time with use of a low speed paper recorder at rates of 1 mm/min and 25 or 50 mm/sec. Audiovisual techniques utilized to detect ventricular ectopic beats included oscilloscopic display of two simultaneous channels of electrocardiographic data and the R-R interval, and use of an R-wave–triggered sound system and an Avionics arrhythmia analyzer. The ability to sweep the tape forward and backward at high speeds facilitated identification of ventricular ectopic beats. The arrhythmia analyzer employing the variable characteristics of prematurity, QRS width and QRS amplitude was individually adjusted for each recording analysis to detect and assess automatically the frequency of ventricular ectopic beats. Frequency, expressed as number of ventricular ectopic beats/hour, was automatically displayed on the electrocardioscanner and charted on a trend printout record indicating the cumulative total of all ventricular ectopic beats hourly. Accuracy of this method for each tape was established by comparison of the arrhythmia analyzer frequency count with a real-time frequency count performed for three separated 5 minute periods in each recording. When accuracy was less than 95 percent, the variable criteria of the arrhythmia analyzer were readjusted until such accuracy was obtained. In two cases 95 percent accuracy of the arrhythmia analyzer could not be achieved and real-time quantitation with hand-counting was performed. In measuring frequency of ventricular ectopy during sinus rhythm these methods have been found to vary from 1 to 2 percent. Additional validation of ventricular ectopic beat frequency count during sinus rhythm was performed by real-time electrocardiographic write-out examination of a randomly chosen hour of each recording. This showed 80 to 90 percent accuracy of ventricular ectopic beat frequency counts. With use of oscilloscopic display and printout validation of two channels of electrocardiographic data, types of ventricular ectopic beats were graded during each hour of recording.

Grading of ventricular ectopic beats during Holter recording has been previously described.[15] The beats are categorized as follows: grade 0 = absence of ventricular arrhythmias; grade 1 = less than 2 ventricular beats/min or 30/hour; grade 2 = 2 or more ventricular ectopic beats/min or more than 30/hour; grade 3 = multiform ventricular ectopic beats; grade 4A = couplets of ventricular ectopic beats; grade 4B = 3 or more consecutive ventricular ectopic beats; and grade 5 = early cycle ventricular ectopic beats with R on T phenomenon. The method of grading ventricular ectopy at high speed playback when compared with real-time writeout of random 1 hour samples was found to be 89 percent sensitive and 100 percent specific.

Additionally, time periods of definite waking activity and sleep were identified by excluding 30 minutes of data before and after diary-recorded entries for sleep, awakening or arising temporarily during sleep and correlating the occurrence of these activities with the expected changes in heart rate indicated on the trend printout record.

Evaluation of Antiarrhythmic Drugs

Response to drug therapy was evaluated by comparing 24 hour Holter recordings obtained before and during a particular antiarrhythmic drug regimen in individual subjects. Drug regimens consisted of oral administration of diphenylhydantoin (600 mg loading dose followed by 100 mg in capsule form every 6 hours); oral administration of propranolol (20 mg in tablet form every 6 hours); oral administration of quinidine sulfate (600 mg loading dose followed by 200 mg in tablet form every 6 hours) and intravenous administration of lidocaine (100 mg bolus injection). Procainamide was not used because of its short half-life, which requires that it be given every 3 to 4 hours and is expected to result in greater noncompliance by asymptomatic subjects. Oral antiarrhythmic regimens were given for 5 days to provide time for optimal drug action before evaluation by 24 hour Holter recordings. Intervals of 1 to 2 weeks without drug treatment were allowed between different drug regimens. Variability of arrhythmia, as assessed by two control 24 hour Holter recordings obtained in most subjects, did not affect maximal grade or mean frequency of ventricular ectopic beats.

Statistical analysis: All data were analyzed and statistical significance computed by chi square analysis or Student's paired t test.

Results

Subjects

Clinical data are presented in Table I. All subjects were asymptomatic when the ventricular ectopy was first noted, most often as an accidental discovery or a finding on routine physical examination. Only one subject (Case 11) could perceive cardiac irregularity with any accuracy, although after discovery of the ectopy, an additional six subjects were intermittently aware of cardiac irregularity in certain body positions. Most subjects were physically active and only five could be classified as sedentary. Three subjects (Cases 6, 15 and 21) were anxiety-prone. A history of rheumatic fever, scarlet fever, diphtheria or major viral illness was lacking in all but one subject (Case 3) who had scarlet fever at age 8 years. A cigarette smoking history was obtained in 16 subjects; only 8 of these were active smokers at the time of evaluation (Table I); the other 8 had discontinued smoking at least 4 years before examination.

Examinations

Physical examination disclosed mild hypertension (systolic 140 to 170, diastolic 100 to 90 mm Hg) in four subjects, early systolic ejection murmurs of grade 1/6 intensity in seven subjects and S_4 gallops in four subjects (the latter all over 50 years of age).

Standard hematologic, urinary and automated screening blood chemistry data were normal. Six subjects (Table I) had fasting hyperlipidemia (cholesterol more than 220, triglycerides more than 150 mg/100 ml). Chest roentgenograms confirmed normal cardiothoracic ratios in all subjects.

Standard 12 lead electrocardiograms revealed ventricular ectopy but were otherwise normal in all except one subject (Case 17), whose tracings disclosed first degree atrioventricular (A-V) block and resting nonspecific S-T segment changes.

Frank lead vectorcardiograms of sinus conducted beats, obtained in 10 subjects, were normal. Vectorcardiograms of ectopic beats with a bundle branch block configuration in seven of these subjects revealed counterclockwise horizontal forces with the main QRS vector directed inferiorly, a pattern consistent with a right ventricular origin.[16,17] Vectorcardiograms of ectopic beats with a right bundle branch block configuration in the remaining three subjects displayed clockwise horizontal forces with the main QRS forces directed inferiorly, a pattern consistent with a left ventricular origin.[18]

Maximal exercise treadmill testing (Bruce protocol) was performed by 23 of 25 subjects. The mean duration of exercise was 8.0 ± 1.8 (standard deviation) minutes, mean maximal heart rate was 161 ± 19 beats/min, and the mean maximal systolic blood pressure was 184 ± 30 mm Hg. Functional aeorbic impairment ranged from −14 to +28 percent and was normal as determined by the Bruce nomogram[19] in all but one subject (Case 14). Apprehension or lack of motivation was a factor in three of five subjects with functional aerobic impairment greater than 20 percent. S-T segment depression without symptoms was recorded during maximal exercise and initial recovery in the one subject (Case 17) who manifested resting S-T segment changes.

Echocardiographic examination of 11 subjects provided technically adequate recordings in 8. Left ventricular and left atrial volumes, left ventricular ejection fraction and mitral valve motion were normal in all 8.

His bundle electrographic studies performed after informed consent had been given revealed normal P-A,

TABLE I

Clinical Data of 25 Apparently Healthy Subjects with Asymptomatic Frequent Complex Ventricular Ectopic Beats (VEB)

Case no.	Age (yr) & Sex	Duration of VEB* (yr)	Cigarette Smoking History	Hypertension	Type of Hyperlipidemia
1	37F	12	. . .	—	—
2	37M	11	+	—	—
3	38M	5	+	—	—
4	39F	1	. . .	—	—
5	42M	3	0	+	—
6	42F	2	+	—	—
7	44M	9	0	—	—
8	45M	2	. . .	+	—
9	47M	12	+	—	II
10	48M	1	0	+	IV
11	49M	2	+	—	—
12	50M	3	0	—	—
13	50M	2	+	—	—
14	50M	1	+	+	IV
15	51F	1	. . .	—	—
16	51M	3	0	—	IV
17	52M	2	0	—	—
18	52M	30	0	—	IV
19	53F	28	. . .	—	—
20	56M	6	+	—	—
21	58F	1	. . .	—	—
22	60M	2	. . .	—	IV
23	64M	1	0	—	—
24	65M	1	. . .	—	—
25	69M	1	. . .	—	—

* Mean duration 6 years.
+ = present; — = absent; 0 = not smoking now; . . . = never smoked.
F = female (mean age 47 years); M = male (mean age 51 years).

A-H and H-V intervals and confirmed the ventricular origin of ectopy in five subjects studied.

Cardiac catheterization, performed in two subjects (Cases 15 and 21) with atypical chest pain that developed after discovery of the ventricular ectopy, revealed normal left and right heart hemodynamic pressures. Angiographic volumes and calculated ejection fractions were normal. Coronary arteriography revealed right coronary arterial dominance in both patients and entirely normal coronary arterial anatomy and distribution.

Ventricular Ectopy

Exercise Testing: Distribution of maximal grades of ventricular ectopic beats during maximal treadmill testing in 23 subjects is illustrated in Figure 1. A subject's maximal grade of ventricular ectopy (defined by exercise testing or Holter recording) was observed during the 3 minute resting control period in 8 subjects and during the postexercise recovery period in 13. Strikingly, 21 of 23 subjects showed complete disappearance of arrhythmia (grade 0) during the last stage of maximal exercise. Low grades of ventricular ectopy (grades 1 and 2) were the most common maximal grades observed during exercise testing, occurring in 65 percent of subjects. Repetitive ventricular ectopic beats (grades 4A and 4B) were more common during the postexercise recovery period. One subject (Case 2) had ventricular tachycardia (grade 4B) during the postexercise recovery period after manifesting grade 2 ventricular ectopic beats during maximal exercise. The majority of maximal and major (grade 3 or higher) grades of ventricular ectopy occurred during the postexercise recovery period (Fig. 1). Functional aerobic impairment, maximal heart rate, maximal systolic blood pressure and peak pressure-rate product during treadmill testing were unrelated to grade or frequency of ventricular ectopic beats in the subjects studied.

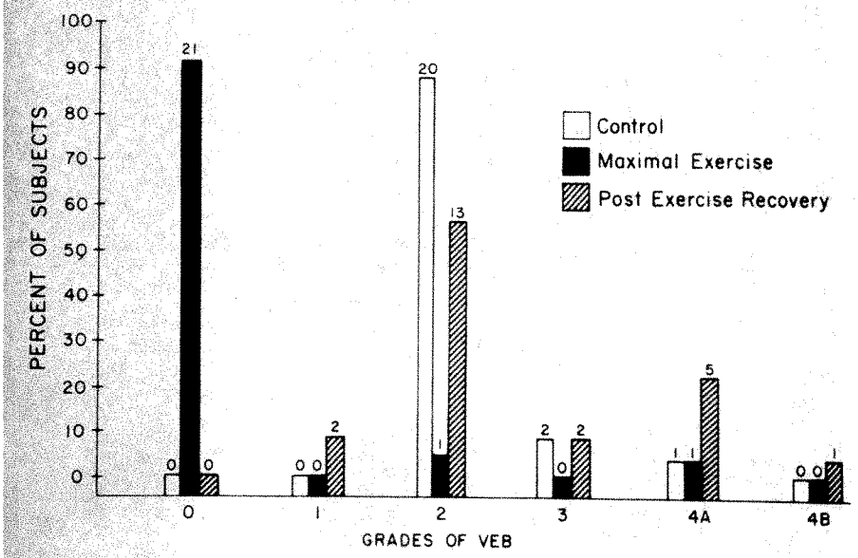

FIGURE 1. Distribution of maximal grades of ventricular ectopic beats (VEB) during a 3 minute control study, maximal exercise and postexercise recovery periods of maximal exercise treadmill testing in 23 subjects.

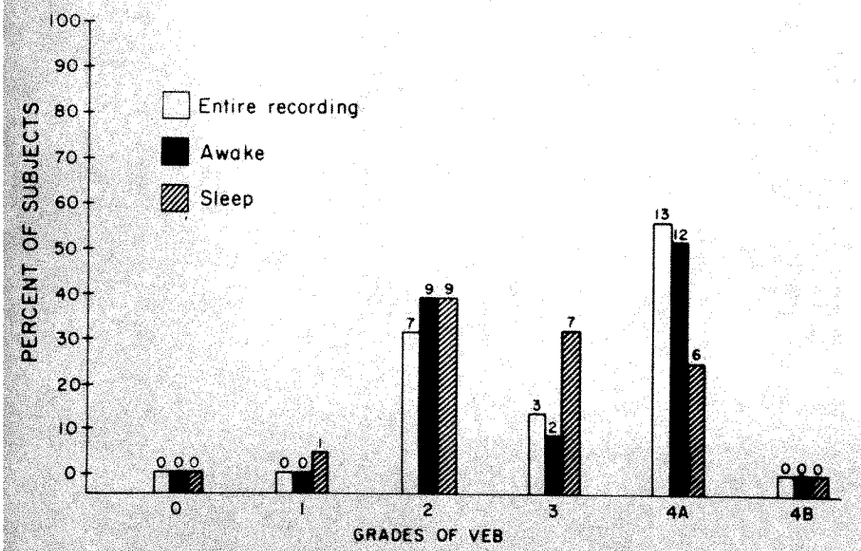

FIGURE 2. Distribution of maximal grade of ventricular ectopic beats (VEB) throughout the entire recording and during waking and sleeping periods of a 24 hour Holter recording in 23 subjects.

Holter recording: Control ambulatory Holter recordings were obtained in all but two subjects (Cases 6 and 19). A total of 1,017 hours of recording data were analyzed from 48 Holter recordings of 23 subjects with definite identification of waking activity for 574 hours and sleep for 308 hours.

Maximal grades of ventricular ectopic beats as detected by Holter recording during a continuous 24 hour diurnal cycle are presented in Figure 2. All subjects studied had the usual hours of waking activity and sleep (that is, no night shift employment). Complex ventricular ectopy was detected in all subjects. A decrease of ventricular couplets during sleep compared with the rate during waking activity or during the 24 hour recording period was associated with an increase in multifocal ventricular ectopic beats during sleep in some subjects. Table II indicates the consistency with which a specific or maximal grade of ventricular ectopic beats occurred. Noteworthy is the consistency with which grades 2, 3 and 4A ventricular ectopic beats were recorded at various hours of study and the paucity of hours without evidence of ventricular ectopy (grade 0). The major grades of ventricular ectopy did not occur sporadically but tended to be consistently present.

The frequency of ventricular ectopy ranged from 0 to 3,103 (mean 559) ectopic beats/hour in the 23 subjects studied. The mean frequency of ventricular ectopic beats during the entire recording period and in the waking and sleeping periods is displayed in Figure 3. Ventricular ectopy increased during activity in 74 percent of subjects, and during sleep in 26 percent of subjects. When the entire recording period is considered, 91 and 70 percent, respectively, of subjects had a mean frequency of more than 100 or 200 ventricular ectopic beats/hour. Consistency of ventricular ectopic beat frequency, allowing for variation with waking activity and sleep, was supported by the close agreement (± 50 ventricular ectopic beats/hour) between the median and mean hourly frequencies of ventricular ectopic beats.

Configurational characteristics of ventricular ectopic beats, recorded in all subjects (by electrocardiogram or Holter recording), indicated a predominantly (70 percent or greater) right ventricular origin (left bundle branch block pattern) in 76 percent (19 of 25) of subjects and a predominantly left ventricular origin (right bundle branch block pattern) in 20 percent (5 of 25); in one subject the ectopic beats originated from the left and right ventricles with nearly equal frequency. Analysis of the QRS configurations of ventricular ectopic beats revealed that four of six subjects who had a right bundle branch block pattern in lead V_1 or MCL_1 had R wave configurations recorded in lead V_5 or CBV_5, indicating a basal origin.[16] Examination of the ventricular ectopic beats of each subject for the characteristics of ventricular parasystole[20] revealed varying coupling intervals in 13 subjects that in 6 reverted to a fixed relation (less than 0.04 second variation) hours later. Ventricular fusion beats were present in nine subjects and mathematically related interectopic intervals in seven subjects; in three of these the intervals

TABLE II

Occurrence of any Specific Grade and Maximal Grade of Ventricular Ectopic Beats (VEB) at 1, 2, 3, 6, and 12 hours of a 24 hr Recording Period (23 Subjects)

Hour of recording	Specific Grade					Maximal Grade				
	0	1	2	3	4A	0	1	2	3	4A
1	5	6	23	15	13	0	0	7	3	13
2	4	4	22	13	11	0	0	7	2	11
3	4	2	22	12	9	0	0	6	1	9
6	1	1	22	10	7	0	0	6	1	7
12	0	1	22	9	6	0	0	6	1	6

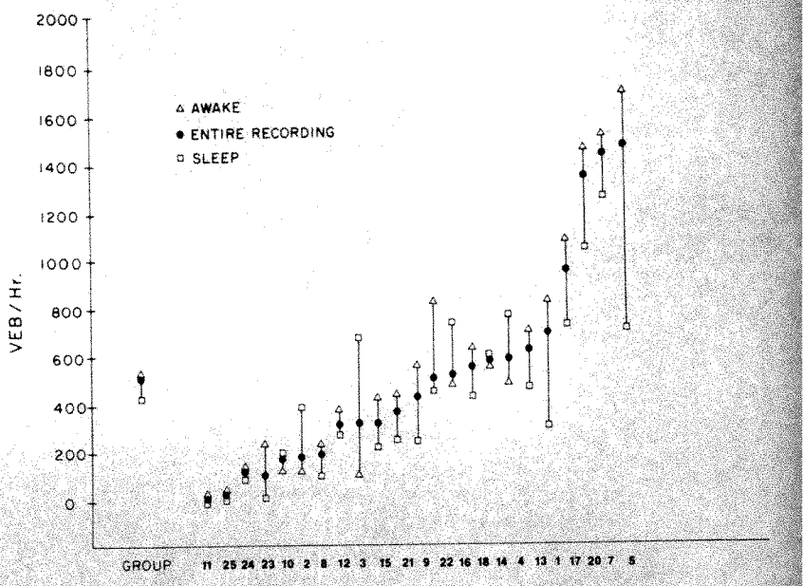

FIGURE 3. Distribution of mean frequency of ventricular ectopic beats per hour (VEB/Hr.) during the entire recording and during waking and sleeping periods of a 24 hour Holter recording in individual subjects and in the group of 23 subjects. Numbers on the abscissa indicate case numbers.

TABLE III

Distribution of Maximal Grade of Ventricular Ectopic Beats During 24 Hour Holter Recordings in Subjects Receiving No Drugs (control) and Antiarrhythmic Regimens of Diphenylhydantoin, Propranolol and Quinidine Sulfate

Antiarrhythmic Drug	Subjects* (no.)	Recorded Hours	Holter Recordings (no.)	Maximal Grade of Ventricular Ectopic Beats					
				0	1	2	3	4A	4B
Control	8	387	18	0	0	3	3	2	0
Diphenylhydantoin	8	178	8	0	0	5	1	2	0
Control	8	435	18	0	0	3	1	4	0
Propranolol	8	192	9	0	0	6	0	2	0
Control	9	425	20	0	0	3	1	5	0
Quinidine Sulfate	9	217	10	0	0	4	0	4	1

* Some subjects received more than one antiarrhythmic drug at different times.

markedly changed hours later without a change in sinus rate or QRS configuration. Only two subjects manifested any two criteria consistently.

Supraventricular arrhythmia, manifested as premature atrial or junctional ectopic beats, occurred rarely in eight subjects. Other dysrhythmias (sinus nodal disease or advanced A-V conduction abnormalities) were not discovered.

Evaluation of Antiarrhythmic Drugs

At the conclusion of each oral antiarrhythmic drug regimen, ambulatory 24 hour Holter recordings were obtained (27 recordings in 12 subjects, Table III). No regimen was associated with a statistically significant decrease in maximal grade of ventricular ectopic beats although a measurable decrease was detected during the propranolol regimen for major grades of ventricular ectopy. Noteworthy was the occurrence of ventricular tachycardia (grade 4B) during treatment with quinidine sulfate in a subject who previously had not exhibited this maximal grade of ventricular ectopy. The hourly frequency of ventricular ectopic beats during antiarrhythmic regimens as compared with control periods is presented in Figure 4. A measurable decrease in frequency occurred during propranolol therapy and a significant decrease ($P < 0.05$) during quinidine sulfate therapy. Although none of the antiarrhythmic regimens used effectively reduced both the maximal grade and frequency of ventricular ectopy, propranolol and quinidine sulfate had limited suppressive effects. Similarly, intravenous lidocaine bolus injection resulted in no significant change in maximal grade or frequency of ventricular ectopic beats in eight subjects studied.

Discussion

Among apparently healthy persons, clinicians often detect latent disease or abnormality. Clinical variables frequently utilized to ascertain "normal" health have commonly included history, physical examination, standard hematologic and blood chemistry examination and chest roentgenogram. More recently, with an appreciation of the dominance of cardiovascular disease in this country, the electrocardiogram and exercise test have become an integral part of the standard assessment of "normal" health. Thus, it seemed reasonable to expect that frequent or complex ventricular dysrhythmia detected by the latter methods in apparently healthy persons would be associated with detectable latent

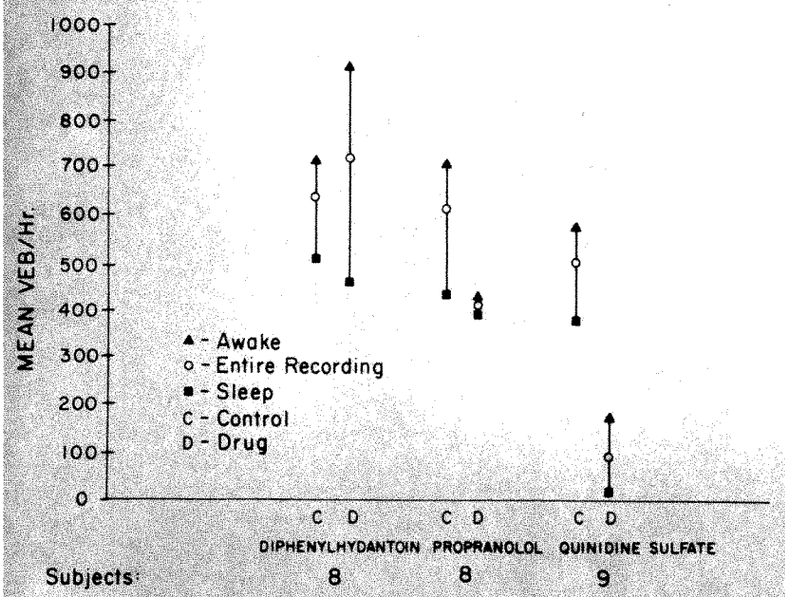

FIGURE 4. Distribution of mean frequency of ventricular ectopic beats per hours (VEB/Hr.) during the entire recording and during waking and sleeping periods of 24 hour Holter recordings taken during control (C) and drug administration (D) in subjects receiving diphenylhydantoin, propranolol and quinidine sulfate regimens.

cardiac disease. This view has been supported by investigators such as Hinkle et al.[3] who stated, "If one defines a 'healthy person' as one who has no evidence of coronary heart disease, hypertension, or chronic obstructive pulmonary disease, and no clinical or [electrocardiographic] evidence of heart disease of any sort, then it can be said that we have rarely, if ever encountered any healthy people with large numbers of [ventricular ectopic beats] in our random samples of middle aged Americans." Other investigators have supported this view.[21] Our study reports on 25 such asymptomatic apparently healthy subjects who manifested both frequent and complex ventricular ectopy, and describes the clinical evaluation of the health of these persons and characteristics of their ventricular ectopy.

Clinical Characteristics

On examination, four of our subjects were found to have mild hypertension; one (Case 17) had electrocardiographic abnormalities in addition to ventricular ectopy and one (Case 14) had an abnormal treadmill exercise performance. Minimal early systolic ejection murmurs and S_4 gallops occurred in four subjects and were not regarded as indicative of disease in three other subjects over 60 years of age. Risk factors have been associated with, but are not necessarily indicators of, coronary heart disease. If one adds subjects with two or more risk factors for coronary heart disease to the six subjects previously identified, only one additional subject (Case 9) would be suspected of having an abnormal cardiovascular status. Thus, we believe that 18 of the 25 subjects had no detectable pathologic or physiologic abnormality other than the presence of frequent complex ventricular dysrhythmia although subclinical disease was not and possibly cannot be excluded. The presentation of apparently normal health and the characteristics of the frequent complex ventricular dysrhythmia suggest that these subjects have a clinical syndrome not previously characterized. Since these findings were present in virtually the entire group, it is reasonable to consider that the detected or speculated abnormalities in the "abnormal" subjects were not a factor in the ventricular ectopy.

Prevalence: The prevalence of this syndrome is unknown, but it has been described in less than 1 percent of young men in electrocardiographic studies[1] and in 19 percent of middle-aged men studied with short-term Holter recordings.[2] Accidental discovery of the asymptomatic ventricular ectopy is most common, and the increased male/female ratio (3:1) is attributed in part to the greater likelihood that men will have a physical examination and electrocardiogram. All subjects but one (Case 24) were white. Age at the time of study ranged from the 4th to the 7th decade, but documented evidence indicated the presence of ventricular ectopy as early as the 3rd decade in some subjects. Typically, these subjects were asymptomatic.

Characterization of the Ventricular Ectopy

The distinctive features of the ventricular ectopy in our subjects included (1) the ectopic QRS configuration, (2) the response of the ectopy to exercise testing, (3) the qualitative type and quantitative frequency of the ectopy, and (4) the consistency of that ectopy. Observations relative to parasystole and antiarrhythmic regimens may also prove useful in identifying subjects with this syndrome.

QRS configuration: Ventricular ectopic beats were predominantly of right ventricular origin as confirmed by electrocardiographic and vectorcardiographic examination. These data and the documented duration of ectopy in some subjects may help support the common view that ventricular ectopic beats of right ventricular origin are generally "benign."

Response to exercise: Strikingly, in 92 percent of subjects all ventricular ectopy disappeared during the last stage of maximal exercise at maximal heart rates. This finding distinctly differs from the usually reported observation of developing or increasing ectopy during maximal exercise in patients with ischemic or other cardiac disease.[6,13,22–24] When compared with data during the control or postexercise recovery period, this finding was highly significant ($P < 0.001$).

Type and frequency of ectopy: Major grades of ventricular arrhythmia were manifested by 70 percent of subjects, with 100 percent having alternating patterns (bigeminy or trigeminy, or both) and 57 percent having repetitive patterns (ventricular couplet). Ventricular tachycardia was infrequent, occurring in one subject in the postexercise recovery period, and early cycle ectopic beats with an R on T phenomenon did not occur. The mean frequency of ventricular ectopic beats during a 24 hour diurnal cycle was greater than 100/hour in 91 percent of subjects and greater than 200/hour in 70 percent. This finding indicates a 4- to 10-fold increase of ectopy over similarly reported data in ambulatory patients with chronic ischemic heart disease.[25]

Consistency of ectopy: Although ectopy generally decreased with sleep in our subjects, as reported in patients with cardiac disorders,[26] the frequency of ventricular ectopy and the consistent appearance of major and maximal grades of dysrhythmia over many hours was distinctive. Thus, the ventricular ectopy in these subjects was not the sporadic disorder found in patients with chronic ischemic heart disease.[22]

Parasystole: Examination of the ventricular ectopy for the criteria of parasystole[20] was perplexing. Varying coupling intervals, detected in more than 50 percent of the subjects, reverted hours later to a fixed relation (without a change in QRS configuration) in half of that group. Mathematically related interectopic intervals, identified in 28 percent of the subjects, often markedly altered hours later without a change in heart rate or QRS configuration. This phenomenon has been reported in both healthy subjects[27] and patients with cardiac disease[25] and seems indicative of the period of ectopy examined rather than of proposed etiologic mechanisms or underlying cardiac abnormality. These observations raise questions with regard to attaching meaningful or prognostic significance[28] to the identification of parasystolic ventricular ectopy.

Effect of therapy: The effectiveness of conventional doses of commonly used antiarrhythmic drugs in our subjects was limited. Only propranolol resulted in a

measurable decrease (not statistically significant) in the maximal grade of ventricular ectopy, and quinidine sulfate caused a significant decrease in the mean frequency of ventricular ectopy. Perhaps larger doses of the antiarrhythmic drugs would be more effective, although a greater incidence of side effects would be expected. In view of the asymptomatic state and lack of objective prognostic data relative to these subjects, a conservative attitude with regard to therapy seems appropriate.

Etiology and Prognosis

The origin of the ventricular ectopy in our subjects is unknown. Recognized causal factors of ventricular ectopic beats resulting from cardiac disease, metabolic or electrolyte disorders, hypoxia, alcohol consumption, excessive tobacco or coffee intake and pharmacologic agents were not identified. Psychologic and neural mechanisms[22] did not seem operative in most subjects. Thus, the genesis of the frequent complex ventricular ectopy remains speculative.

The pathologic significance of the ventricular ectopy in our subjects may become clearer as a result of additional cohort investigative and natural history prospective studies now in progress. The prognostic significance of this arrhythmia, frequently regarded as ominous by clinicians, is undefined. We believe that the prognosis in such subjects is related not only to the type and frequency of the ventricular ectopy but also to the underlying state of the heart affected by it, and the psychologic, neural and humoral environment in which it occurs.

Thus our study adds additional data to a growing body of knowledge of cardiac dysrhythmia and focuses attention on a group of apparently healthy subjects who display a characteristic clinical syndrome of frequent complex ventricular ectopy.

Our study also calls attention to information that could be obtained by using sensitive detection methods to conduct a sizable survey of cardiac dysrhythmia in ostensibly normal persons, as suggested by other investigators.[2,15,22] The distinction between "apparently healthy" persons with subclinical disease and "normal" persons with physiologic or physical irregularities is sometimes obscured by clinical bias. It can be clearly established only by defining the prevalence, incidence and natural history of irregularities examined within a population and establishing associations with pathogenic mechanisms, if any exist.

Acknowledgments

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Sinus Bradycardia and Atrial Fibrillation Associated With the Wolff-Parkinson-White Syndrome

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Thirty-three patients with atrial fibrillation associated with the Wolff-Parkinson-White (WPW) syndrome were studied to determine the relation of sinus bradycardia and atrial fibrillation. In seven patients the sinus rate was less than 40 beats/min and sinus nodal disease was considered a cause of the periods of bradycardia. Ventricular fibrillation or functional cardiac arrest was documented in four instances. Twenty-six patients demonstrated a type A and seven a type B WPW pattern during periods of sinus rhythm. Male patients predominated. The average age was 38.5 years among patients with a type A pattern compared with 25.3 years among those with a type B pattern. The shortest R-R cycle length in this group was 130 msec during a period of atrial fibrillation. Five thousand serial microscopic sections were studied in one patient who demonstrated ventricular fibrillation. Three anomalous pathways were located in this patient with the widest tract, 380 μ, containing about 400 muscle cells. Most of the sinoatrial node was replaced by collagen elastic fibers, and there was widespread destruction of the atria with a marked increase in fibrous connective tissue.

Ventricular fibrillation or functional cardiac arrest is not a rare arrhythmia in patients with atrial fibrillation associated with the WPW syndrome and may be responsible for sudden death in patients with these arrhythmias. Hence, precise electrophysiologic studies and pharmacologic or surgical management, or both, are suggested to prevent sudden death in patients with short refractory periods associated with atrial fibrillation and the WPW syndrome.

In 1930, Wolff et al.[1] described a syndrome characterized by "bundle branch block and a short P-R interval in healthy young people prone to paroxysmal tachycardia." In the years following, an abundance of anatomic and electrophysiologic information has further elucidated the nature of ventricular preexcitation and the mechanisms responsible for the tachycardias associated with the Wolff-Parkinson-White (WPW) syndrome.[2–12] The frequent episodes of paroxysmal supraventricular tachycardia can probably, in most instances, be ascribed to circus movements using both normal and anomalous atrioventricular (A-V) pathways.[4] The tachycardias are usually self-limited. In certain patients with refractory circus movement arrhythmias, electrophysiologic studies[4,6,7] may unravel the mechanism of tachycardia and provide a basis for better pharmacologic control.[13–15] In other instances, surgical interruption of either the anomalous pathways[16–18] or the A-V junction[5] has been necessary to control the tachycardia syndrome.

In some patients, atrial fibrillation or atrial flutter can be associated with the WPW syndrome; sudden death has been reported in some instances.[19–21] Boineau and Moore[22] repeatedly produced ventricular fibrillation in response to rapid atrial stimulation in a dog with preexcitation. Wellens and Durrer[23] were able to correlate the refractory period

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of the anomalous pathway and the ventricular rate in patients with atrial fibrillation. Atrial fibrillation is not a rare arrhythmia in the WPW syndrome; Laham[24] reported an 11.5 percent incidence rate. Type A conduction appeared to predominate over type B in his cases, as well as in several other series that he reviewed.

TABLE I
Data in 33 Cases of WPW Syndrome Associated With Atrial Fibrillation

Case no.	Age (yr) & Sex	Diagnosis	Type WPW
1*	62F	ASHD, SSS	A
2*	12M	...	A
3*	26F	...	A
4*	26M	...	A
5	41M	RHD	A
6	52F	RHD	A
7	46M	RHD	A
8	58F	CAD	A
9	46M	CAD	A
10	43M	SSS	A
11	27M	SSS	A
12	23M	...	A
13	46F	...	A
14	27M	...	A
15	54F	...	A
16	21M	...	A
17	36M	...	A
18	41M	...	A
19	23M	...	A
20	35M	...	A
21	57M	ASHD, SSS	A
22	50M	SSS	A
23	18F	...	A
24	50M	...	A
25	42F	...	A
26	50M	...	A
27	23M	...	B
28	15M	SSS	B
29	30F	...	B
30	40F	SSS	B
31	12M	...	B
32	45M	...	B
33	23M	...	B

* Patient had ventricular fibrillation or functional cardiac arrest.
ASHD = arteriosclerotic heart disease; CAD = coronary artery disease; RHD = rheumatic heart disease; SSS = so-called sick sinus syndrome.

Dreifus et al.[25] suggested that this association could be correlated with the sick sinus syndrome. In short, the tachycardia-bradycardia syndrome, especially atrial fibrillation associated with sinus nodal and intraatrial disease, may accompany WPW conduction. Consequently, a study was made of 33 patients with WPW conduction associated with atrial fibrillation. In one previously reported case,[21] a careful study of the pathologic anatomy was possible 2 years after documentation of ventricular fibrillation.

Materials and Methods

A combined group of 33 consecutive patients was referred to us for evaluation of the WPW syndrome with an associated documented history of atrial fibrillation (Table I). All 33 patients had spontaneous periods of atrial fibrillation; 5 had atrial flutter as well. Twenty-six type A and seven type B WPW electrocardiographic patterns were recorded during periods of sinus rhythm. The patients with a type A pattern were 19 male and 8 female subjects with an average age of 38.5 years. The average age of the patients with type B conduction was 25.3 years. In seven patients, the sinus rate was documented as less than 40 beats/min in at least one 12 lead electrocardiogram or monitor tracing (Fig. 1). Continuous electrocardiographic strips or Holter monitor readings were not routinely made.

Ventricular fibrillation or functional cardiac arrest was documented in four patients (Cases 1 to 4, Fig. 2 to 4). All four were resuscitated with electric cardioversion. Functional cardiac arrest was diagnosed when the ventricular rate produced circulatory arrest (Cases 2 and 4, Fig. 3 and 4B). The precise moment of transition from a rapid ventricular rate in response to atrial fibrillation to ventricular fibrillation could not always be established (Fig. 3 and 4B). Case 1 was previously cited[21] to document ventricular fibrillation after atrial fibrillation (Fig. 2). This patient died 2 years later of metastatic breast cancer. The heart was recovered at necropsy and prepared for a microscopic serial section study. The anatomic and histologic data are presented in an attempt to correlate electrocardiographic findings with the associated mechanisms that resulted from sinus node disease, atrial fibrillation and ventricular fibrillation. The remaining 32 patients in this series are alive.

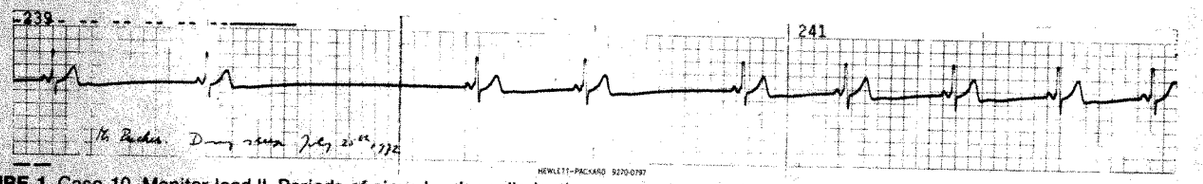

FIGURE 1. Case 10. Monitor lead II. Periods of sinus bradycardia lasting up to 4.2 seconds were noted during continuous monitoring.

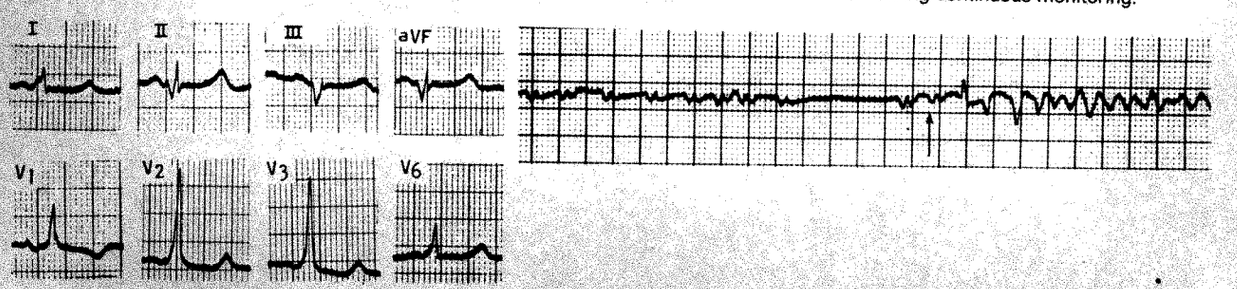

FIGURE 2. Case 1. **Left,** standard electrocardiographic leads. **Right,** atrial fibrillation followed by ventricular fibrillation. The shortest cycle length **(arrow)** is 180 msec.

Results

The four patients with one or more periods of ventricular fibrillation or functional cardiac arrest were successfully resuscitated before appropriate pharmacologic management was achieved. The shortest R-R cycle length was 180 msec in Case 1 (Fig. 1), 140 msec in Cases 2 and 3 and 130 msec in Case 4 during a period of atrial fibrillation (arrow, Fig. 4B). The frequent occurrence of R on T phenomenon is apparent in the presence of these short cycle lengths.

Case 1

The main portions of the cardiac conduction system in Case 1 were included in 11 tissue blocks from this heart. Microscopic examination of the 5,000 stained serial sections revealed interesting histologic and pathologic details pertinent to the antemortem history.

Accessory tracts: Three accessory muscle bridges crossed the atrioventricular (A-V) junction to connect the left atrium with the ventricular myocardium. The diagram in Figure 5 depicts the locations of these three anomalous muscle pathways (1 to 3). Tract 1 was 300 μ wide and extended through 39 sections (390 μ) to connect the posterior wall of the left atrium with the top of the interventricular septum. Figure 6 demonstrates the other two accessory A-V muscle bridges (tracts 2 and 3) at the junction between the left atrial myocardium and lateral posterior wall of the left ventricle. The second and third accessory tracts were located in an extreme lateral position near the lateral commissure of the mitral valve. Tract 2 was 380 μ wide and extended through 123 serial sections (123 μ) as it connected the posterior myocardial walls of the left atrium and left ventricle. At its widest point, tract 2 contained about 400 muscle cells and was considered a large incursion of atrial fibers into the ventricle. Accessory bundle 3 had the same myocardial connections as bundle 2, but was somewhat nearer the endocardial attachment of the mitral

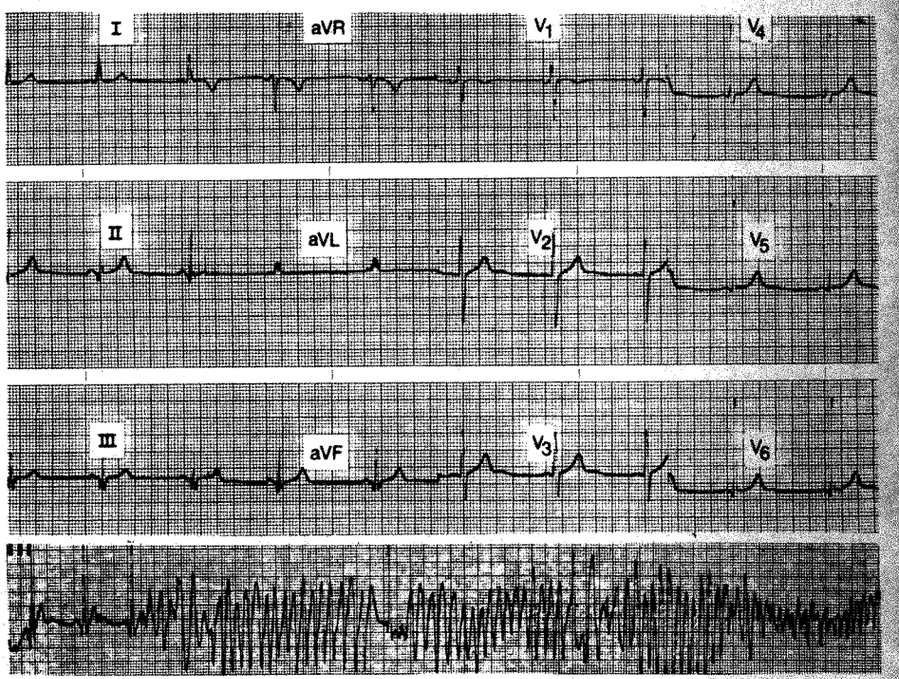

FIGURE 3. Case 2. **Upper strips,** 12 lead electrocardiogram. **Lower strip,** lead III, showing onset of atrial fibrillation and functional cardiac arrest, probably due to atrial fibrillation and ventricular fibrillation. The shortest cycle length is 160 msec.

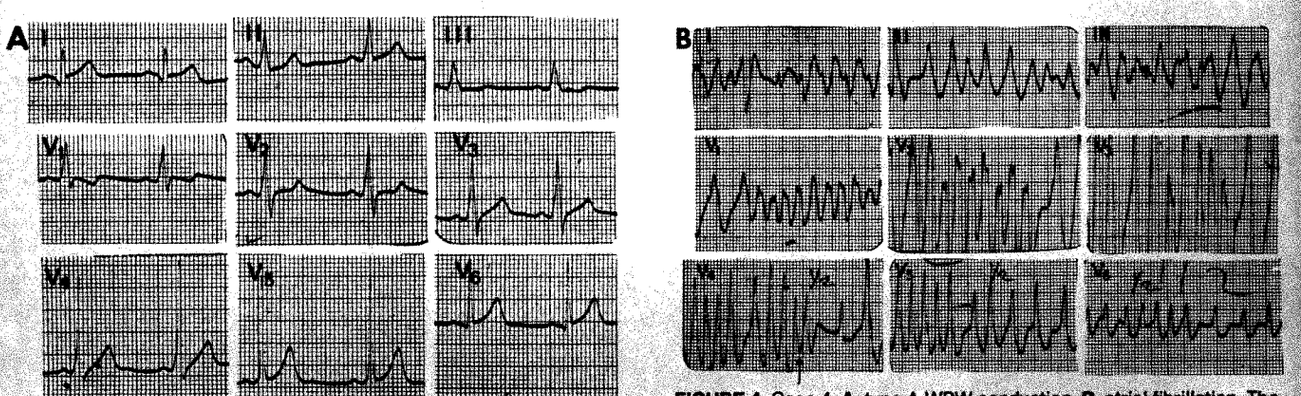

FIGURE 4. Case 4. **A,** type A WPW conduction. **B,** atrial fibrillation. The shortest R-R interval is 130 msec (**arrow** in lead V_4).

valve. Tract 3 was 330 μ wide and extended through 243 serial sections (2,430 μ). At its widest point, this tract contained about 200 muscle cells. All three accessory muscle bridges had the histologic features of atrial muscle cells as they crossed the A-V junction to join ventricular muscle. The anatomic location and relations of these three tracts would have made them amenable to surgical interruption had their locations been determined by current mapping techniques.

Atria and S-A node: *The myocardium* of all four chambers showed cardiac disease and there was severe disease in both the atria (Fig. 7 and 8) and ventricles (Fig. 9). Most of the sinoatrial (S-A) nodal cells had been replaced by collagen and elastic fibers. The portion of the S-A node shown in Figure 7 contained the greatest number of nodal cells found throughout the entire node. In most of the sections, only a few isolated nodal cells were observed around the nodal artery. The destruction of S-A nodal cells with subsequent replacement fibrosis observed in this case is similar to, but more severe than, that described in older patients[27] or patients with systemic lupus erythematosus.[28] The myocardial cells of both atria as well as the interatrial septum showed abnormal nuclei, hypertrophy and a marked increase in fibrous connective tissue. In many areas large pale atrial cells were undergoing fat necrosis and degeneration (Fig. 8). Warner et al.[29] recently observed myocardial necrosis and fibrous scars 3 to 14 days after multiple transthoracic defibrillator countershocks delivered to experimental animals. Although our patient had more than one antemortem defibrillation 2 years before her death, we are unable to say how much of the atrial muscle necrosis and fibrosis (Fig. 8) was secondary to antemortem countershock. The myocardium of the atria, especially that of the interatrial septum, contained large numbers of multilocular (fetal, brown) fat cells. The endocardium was fibrotic and thickened in both atria, as was the endocardium of the left ventricle.

Coronary arteries and ventricular myocardium: Atherosclerosis was present in most of the small arteries of the ventricular myocardium, particularly those in the left ventricle and interventricular septum. The walls and papillary muscles of the left ventricle showed widespread areas of muscle cell destruction and replacement fibrosis as a result of healed myocardial infarctions. Figure 9 shows microscopic evidence of three successive vascular episodes as numbered 1, 2, and 3. The first infarction interrupted part of the posterior fascicle of the left bundle branch in the subendocardium. This area is now composed of dense contracted scar tissue and some remaining macrophages. A second infarcted area (2, Fig. 9) is fibrous but less dense and contains many more macrophages with engulfed debris. The most recent area of infarction (3, Fig. 9) with less formed connective tissue fibers is adjacent to ischemic muscle cells, some of which show evidence of degeneration. The preservation of viable ventricular muscle cells (arrows) around some of the tributaries (t) of a Thebesian vein (v) indicates that such vessels may afford collateral routes to, and play a nutritive role for, the immediately adjacent ventricular muscle cells after myocardial infarction.

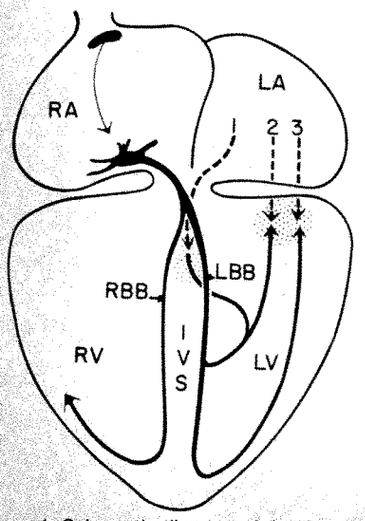

FIGURE 5. Case 1. Schematic diagram of the three accessory A-V pathways (1, 2 and 3) demonstrated by microscopic serial sections. IVS = interventricular septum; LA = left atrium; LBB = left bundle branch; LV = left ventricle; RA = right atrium; RBB = right bundle branch; RV = right ventricle.

Discussion

The tachycardia-bradycardia syndrome and sinus node and intraatrial disease with WPW: In recent years, sinus nodal disorders have been identified as a basis of Adams-Stokes attacks. The general term "sick sinus syndrome" has been used to include numerous sinus and atrial rhythm disturbances.[26,27] Kaplan et al.[27] have argued that these several conditions

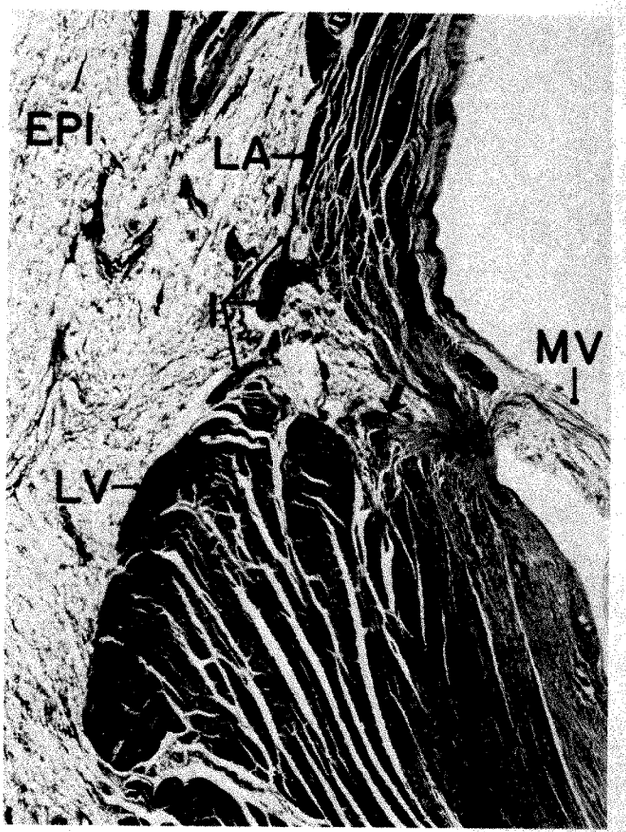

FIGURE 6. Case 1. Two accessory A-V muscle bridges at the junction between the myocardium of the left atrium (LA) and the lateral posterior wall of the left ventricle (LV). One accessory bundle (1) lies adjacent to the epicardium (EPI), and its muscle fibers are identified here with some of the atrial attachments. A second accessory bundle (indicated by **the short thick arrow**) is close to the endocardial attachment of the posterior leaflet of the mitral valve (MV). (Hematoxylin-phloxine-saffranin stain ×15, reduced by 25 percent.)

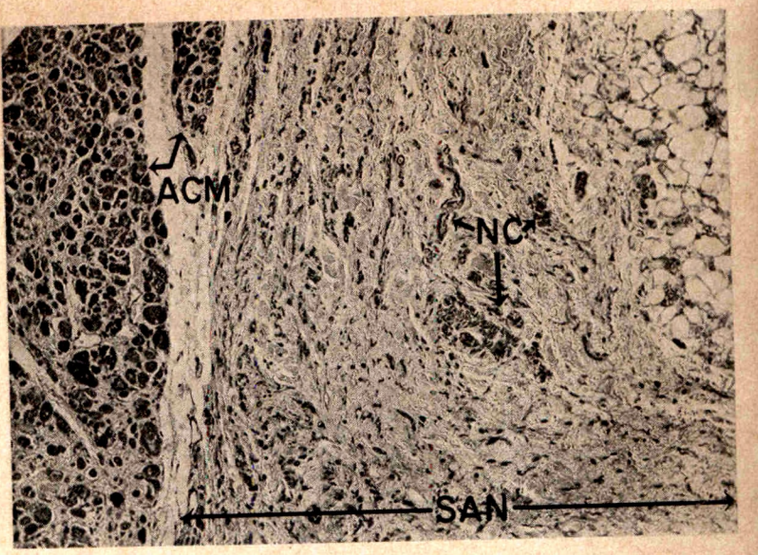

FIGURE 7. Case 1. Microscopic section through superior part of S-A node (SAN) and adjacent atrial cardiac muscle (ACM). Small bundles of nodal cells (NC) are isolated in a sea of collagen fibers and fibroblast nuclei. Fat cells of the epicardium appear on the right side of the photomicrograph. (Holmes silver stain ×142, reduced by 38 percent.)

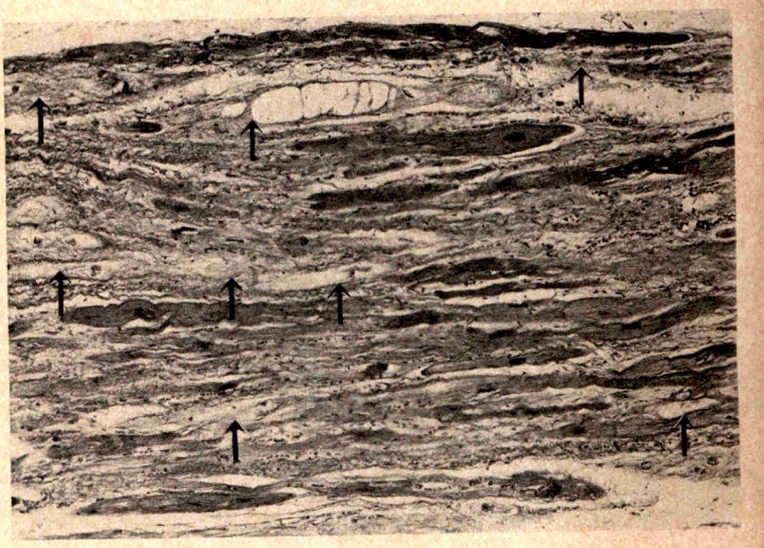

FIGURE 8. Case 1. Hypertrophied left atrial muscle cells with pyknotic nuclei surrounded by increased amounts of fibrous connective tissue. Note the large pale muscle cells in different stages of fat necrosis (**arrows**). (Hematoxylin-phloxine-saffranin stain ×142, reduced by 38 percent.)

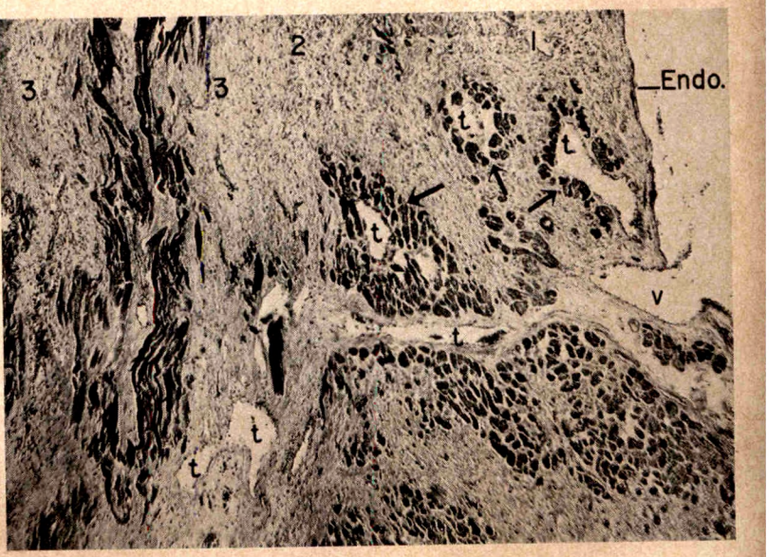

FIGURE 9. Case 1. Interventricular septum with two old (1, 2) and one recent area of myocardial infarction (3). Note preservation of muscle cells (**arrows**) immediately adjacent to a Thebesian vein (v) and its several tributaries (t). Conduction cells of the left bundle branch were destroyed as they coursed distally in the subendocardium (Endo.) of the left ventricle. (Masson trichrome stain ×50, reduced by 38 percent.)

are likely to be interrelated and that more than one arrhythmia may be present at different times in the same patient. They have considered several electrocardiographic mechanisms as part of this entity: (1) sinus arrest, including atrial standstill; (2) sinoatrial (S-A) block; (3) failure of the sinus rhythm to follow promptly electric conversions of atrial flutter; (4) marked sinus bradycardia with or without atrial premature systoles; (5) chronic atrial fibrillation with a slow ventricular rate not drug-induced; (6) sinus bradycardia, with recurrent paroxysmal atrial fibrillation; and (7) tachycardia-bradycardia syndrome. In fact, 9 of their 10 cases demonstrated atrial fibrillation. The identification of sinus bradycardia in several patients with the WPW syndrome and atrial fibrillation suggests that some of these patients not only have accessory pathways but other disease as well (for example, of the nodes, myocardium, endocardium or blood vessels). Hence, it is not unrealistic to speculate that bradycardia-tachycardia syndromes can be associated with a variety of conduction disorders.

Hindman et al.[30] discussed the high frequency of sinus bradycardia and sinus arrhythmia and the occurrence of A-V dissociation and A-V nodal escapes as well as sinus arrest observed during portable monitoring of patients with WPW conduction. They implied the existence of conduction disease in addition to accessory tracts or functional bypass of the A-V node. The marked changes in and around the sinus node as well as atria and ventricles of Case 1 support this hypothesis, for this patient with WPW conduction also demonstrated atrial fibrillation and ventricular fibrillation.

Relation of other supraventricular arrhythmias to atrial flutter and atrial fibrillation in the WPW syndrome: Durrer et al.[3] have shown that tachycardias associated with WPW conduction can be initiated or terminated by appropriately timed premature activation of either the atria or the ventricles. The timing of these premature systoles in relation to refractory periods of the normal A-V conduction system, as well as the accessory pathways, will determine the pathway of circus movement between the atria and ventricle. Dreifus et al.[5] had previously shown that both the normal A-V conduction system and the accessory pathway are necessary for the genesis of such tachycardias. Ligation of the A-V pathway promptly eliminated recurrence of the tachycardias. Hindman et al.[30] documented the large incidence of premature systoles during normal daily activity in patients with WPW conduction. This is important in view of the known role of premature beats in the initiation of reentry tachycardias and atrial fibrillation in patients with preexcitation.

Atrial and ventricular premature systoles may result in only a circus movement tachycardia. However, a premature atrial systole or retrograde conduction of an impulse from the ventricles to the atria may arrive during the atrial vulnerable period and thereby initiate atrial flutter or atrial fibrillation. Also, circus movement tachycardia may deteriorate into atrial fibrillation. Atrial flutter or fibrillation can be produced by extrastimulus techniques; therefore, one should be prepared for the possibility that atrial fibrillation will lead to ventricular fibrillation in these patients during electrophysiologic studies.

Pathways of conduction and regulation of ventricular rate during atrial flutter and atrial fibrillation: Both the normal A-V conduction system and the accessory pathways can transmit rapid atrial impulses to the ventricles; hence, the use of one or both pathways depends upon rather precise electrophysiologic principles.[31] Although the functional refractory period of the accessory pathway is frequently shorter than that of the normal A-V system, other factors, such as concealed conduction into one or the other pathway, may force the impulse either exclusively through one pathway or through both pathways simultaneously.[3] For example, if the functional refractory period of the accessory pathway is significantly shorter than that of the normal A-V conduction system, it should logically result in conduction of all atrial impulses to the ventricles by way of the accessory pathway.[23] However, repetitive concealment within the accessory pathway may force the impulse through the normal A-V conduction system intermittently or, in some instances, exclusively. In some cases, nearly all supraventricular impulses reach the ventricles exclusively or predominantly through the accessory pathway in the presence of atrial fibrillation, and the resulting QRS complexes show either a pure WPW contour or one distorted by incomplete ventricular recovery.[23,25,32] Hence, these rhythms have often been erroneously identified as ventricular tachycardias whereas they are really supraventricular mechanisms associated with WPW conduction. In 1970 Castillo and Castellanos[6] suggested that the persistence of atrial flutter and fibrillation could be attributed to coexisting atrial disease. This hypothesis is supported by the anatomic and pathologic findings in our Case 1. It has been clearly documented that patients with atrial fibrillation in the presence of accessory pathways can die suddenly because of ventricular fibrillation.[19–21]

In most cases, regulation of the ventricular rate during atrial fibrillation in the WPW syndrome hinges upon the functional refractory period of the normal and the anomalous A-V pathway.[23] Castellanos et al.[32] used premature atrial stimulation to study six patients with the preexcitation syndrome. Ventricular rates during bursts of atrial flutter and atrial fibrillation depended on the functional properties of the accessory pathway. In three patients whose effective refractory period of the accessory pathway was longer than that of the A-V pathway, the ventricular rates did not exceed 210 beats/min. Most of the supraventricular impulses apparently reached the ventricles through the normal A-V conduction system. However, in three other patients the refractory period of the accessory pathways was very short (less than 220 msec). In these patients the ventricular rates were as high as 310/min and most of the impulses reached the ventricles through the accessory pathways. These authors noted that multiple concealed A-V conduction occurred in both pathways, producing R-R pauses well in excess of the duration of the corresponding effective refractory periods. They further

concluded that atrial fibrillation and flutter were due to stimulation during the atrial vulnerable period and not to a reciprocating mechanism involving two separate anatomic A-V communications.

Wellens et al.[23] have identified factors that determine the ventricular rate during atrial fibrillation. Most pertinent was the finding that the duration of the effective refractory period of the accessory pathway correlated with the shortest R-R interval and the mean ventricular rate during atrial fibrillation. In four of our patients (Cases 1 to 4, Table I) the R-R interval was 180 msec or less; in Case 4, it was as short as 130 msec. We noted functional cardiac arrest or ventricular fibrillation in all four of these patients, but the ultimate fate of the other patients with a very short R-R cycle is unknown. Functional cardiac arrest was reported by Coskey and Danzig[33] in a 17 year old high school student during jogging: the shortest R-R interval during atrial fibrillation in this student was 160 msec. It is difficult in this case, as well as in our Cases 2 and 4, to identify accurately the onset of true ventricular fibrillation, since the rapid ventricular response in atrial fibrillation with aberrant ventricular conduction appears similar. However, functional cardiac arrest and sudden death are inevitable unless immediate cardioversion is performed.

Possible mechanism of ventricular fibrillation: Moore and co-workers[9,22] documented the onset of ventricular fibrillation in the dog, and similar observations have been made in man.[21] If ventricular fibrillation develops in response to high atrial rates, the arrival of the impulse in the ventricles during the vulnerable period must be considered. R on T beats are frequently observed. To understand fully the possible pathophysiology of ventricular fibrillation in these instances, it must be recognized that the accessory pathways are actually communications between atrial tissue and the ventricular myocardium.[34] The anatomic data presented in our study support this concept. Under these circumstances, high atrial stimulation rates could invade the neighboring ventricular fibers during ventricular vulnerability and engender ventricular fibrillation. Ventricular depolarization in these circumstances would be dependent upon several factors: (1) the refractory period of the ventricular tissues surrounding the atrial incursion; (2) organization of the wave front of atrial impulses traversing the accessory pathway; and (3) inhomogeneous conduction within the ventricular myocardium. One or more of these predisposing factors could lead to further conduction abnormalities and ventricular fibrillation. The advanced ventricular myocardial and endocardial disease in our Case 1 (Fig. 9) could have contributed to ventricular fibrillation. Cardiac disease was severe in both the atria and the ventricles and could have contributed to sinus arrest and atrial fibrillation as well as ventricular fibrillation. The major portion of the S-A node was completely destroyed and was replaced by collagen and elastic fibers (Fig. 7). These microscopic changes in myocardial structure participated in functional aberrations of atrial and ventricular conduction that could culminate in ventricular fibrillation. It should be noted also that the average age of patients with type A WPW conduction with atrial fibrillation was greater than that of patients with type B conduction.

Clinical implications: This study of patients with the WPW syndrome and atrial fibrillation suggests that a short refractory period within the accessory pathway could contribute to the risk of ventricular fibrillation or functional cardiac arrest, or both. Sudden death in young persons with the WPW syndrome might be explained on this basis. One large accessory pathway or multiple small pathways associated with short refractory periods might have increased vulnerability to ventricular fibrillation once atrial fibrillation was established. The association of tachycardia-bradycardia syndrome in these patients is very likely the result of sinus node and atrial disease. Such was true in Case 1 and similar disease could explain the electrocardiographic changes in two other patients[34] who died suddenly with the WPW syndrome associated with supraventricular tachycardias other than atrial fibrillation. Young persons with the WPW syndrome should be carefully evaluated for tachycardia-bradycardia syndromes, particularly if they are engaged in competitive sports. Older patients with the WPW syndrome require careful evaluation in order to delineate superimposed vascular and myocardial lesions that may prompt sudden, unexpected death. Patients with recurrent atrial fibrillation associated with an extremely short A-V refractory period should be given precise pharmacologic regimens to increase the refractory period of the bypass tract. Patients 1 and 4 were managed with orally administered procainamide plus propranolol. A demand pacemaker was implanted in Case 1 because of periods of sinus arrest. After an unsuccessful attempt to interrupt surgically the accessory pathways in Case 3, the patient was controlled with orally administered procainamide. Patient 10 underwent successful surgical intervention of the bypass tract after electrophysiologic mapping of the heart.

Precise electrophysiologic studies are required to identify optional treatment programs.[15] Digitalis may shorten refractoriness of the accessory pathway and thus be hazardous for some patients.[15] Quinidine, procainamide and ajmaline are effective in increasing the refractory period of the accessory pathway[13] and may offer an important approach to pharmacologic management of patients with the WPW syndrome. Rosenbaum et al.[35] recently showed that amiodarone was effective in lengthening the refractory period of the accessory pathway. In the presence of symptomatic bradycardia it may be necessary to implant a pacemaker, as in our Case 1.

Patients not responding to pharmacologic programs should be considered for surgical management. Precise electrophysiologic mapping of the heart must precede attempts to interrupt surgically the accessory pathways.[17]

Acknowledgment

We are indebted to Dr. Leonard Scherlis for permission to include Case 3 in this series.

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Long-Term Evaluation of Early Repolarization Syndrome (Normal Variant RS-T Segment Elevation)

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The electrocardiograms of 65 patients with the "early repolarization syndrome" (normal variant of RS-T elevation) were analyzed to delineate the features and evaluate the natural history of this electrocardiographic entity. Maximal follow-up was 26 years. The syndrome was characterized by (1) an upward concave elevation of the RS-T segment with distinct or "embryonic" J waves, slurred downstroke of R waves or distinct J points or both; (2) RS-T segment elevation commonly encountered in the precordial leads and more distinct in these leads; (3) rapid QRS transition in the precordial leads with counterclockwise rotation; and (4) persistence of these characteristics for many years although some intraindividual changes were common. Less commonly found were (5) tall R and T waves in the precordial leads; (6) "labile" or "juvenile" T wave patterns; (7) "pseudo-R'" waves; and (8) "isolated T negativity syndrome." These changes commonly simulate pericarditis, myocardial ischemia, left ventricular hypertrophy and right bundle branch block.

It is well recognized that electrocardiograms of apparently normal persons may show RS-T segment elevation mimicking cardiac disease. This form of RS-T elevation was reported first by Shipley and Hallaran,[1] then by Meyers et al.[2] and Goldman,[3] and commonly termed "early repolarization".[4] Wasserburger et al.[5] summarized the electrocardiographic characteristics of this normal variant as the following (Fig. 1): (1) an elevated take-off of the S-T segment at the J junction of the QRS complex; (2) a distinct notch or slur on the downstroke of the R wave; (3) an upward concavity of the S-T segment; and (4) symmetrically limbed T waves that are often of large amplitude. This pattern occurs in approximately 2 percent of adults[6] and appears to be most commonly encountered in young black adults[3,7–13] although there has been some disagreement about racial variation.[14–16]

The purpose of this study was to characterize the quantitative and qualitative variations of this "early repolarization syndrome," evaluate long-term variations (natural history) and describe the electrocardiographic similarities to pericarditis, myocardial injury, left ventricular hypertrophy, and even right bundle branch block.

Materials and Methods

The Electrocardiographic Station at the Veterans Administration Hospital in New Orleans has maintained a file of electrocardiograms on all patients since 1943. From these files, the cases of all patients whose electrocardiograms were classified as showing "early repolarization" and whose serial electrocardiograms were available over a minimum of 5 years were reviewed. The electrocardiograms of 65 patients were analyzed over an average period of 11 years (maximum 26 [Fig. 2], minimum 5). All patients studied were male, and 52 of the 65 were black. Their ages ranged from 22 to 80 years; 70 percent were aged 30 to 59 years.

To be termed "early repolarization" and included in this study, RS-T segment elevation had to be a minimum of 0.5 mm above baseline in at least two limb or precordial leads. Displacement of the RS-T segment was measured from the lowest point of the segment to a baseline constructed by aligning a straight line

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with the successive T-P segments. When the latter were obscured by tachycardia, the terminal portion of the preceding P-R segment was used for the baseline. The height of the J waves, J points and T waves was also determined from this baseline, and a notch on the downstroke of the QRS complex was considered the tip of the J wave (termed "embryonic J wave") when a well defined bifaceted J wave was not present. The transitional area from the QRS complex to the S-T segment was further characterized as "slurred" when the R wave was gradually transformed to the S-T segment with upright concavity and as "distinct J point" if a sharp angling point was noted. Apparent R′ waves in leads V_1 and V_2 were termed "pseudo-R′" when unassociated with a rightward terminal vector in the limb leads.

Results

RS-T elevation: This was encountered most frequently in leads V_3 (80 percent of cases) and V_4 (80 percent), then in leads V_2 (66 percent) and V_5 (60 percent) (Fig. 2). Among the limb leads, it was most prevalent (15 percent) in lead I. No patient had RS-T elevation in lead aVR. The greatest mean RS-T elevation (Fig. 2) and the maximal elevation (5 mm, Fig. 3) was noted in lead V_2. Correlation of the greatest RS-T displacement in the precordial leads with that in the limb leads, based on analysis of one tracing from each patient that was most characteristic of the "early repolariza-

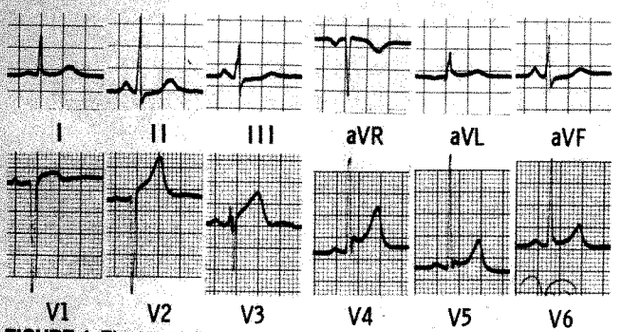

FIGURE 1. Electrocardiogram of a 30 year old black man without known cardiovascular disease showing typical characteristics of the "early repolarization" syndrome. Note the characteristic "rapid transition zone" in leads V_3 to V_4, the prominent J waves leads (leads V_4 and V_5) and slurring downstroke of the R waves in lead V_6.

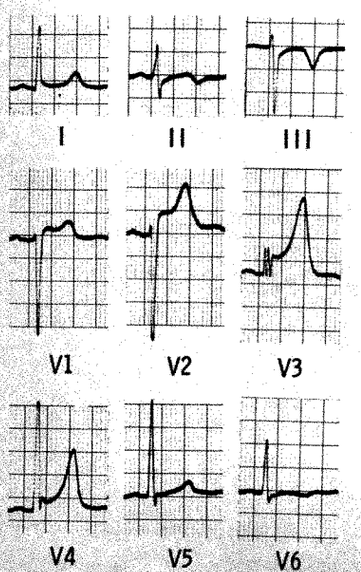

FIGURE 3. Electrocardiogram of an asymptomatic 33 year old black man revealing 5 mm RS-T elevation in lead V_2 and 4 mm elevation in lead V_3. The patient had no clinical evidence of heart disease.

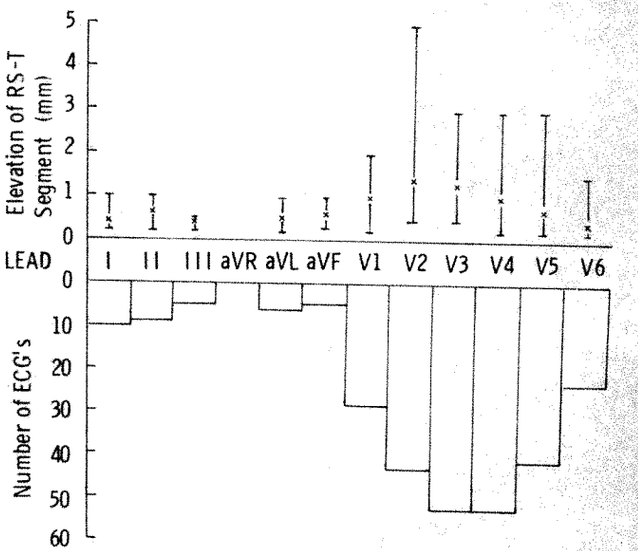

FIGURE 2. Frequency and magnitude of RS-T segment elevation in each lead of the electrocardiogram (ECG). Sixty-five electrocardiograms, one from each patient that was most typical of the "early repolarization" syndrome, were analyzed. The frequency of RS-T elevations in the respective leads is shown in the **bottom bar graph** and the magnitude of elevation is shown at **top. Crosses** indicate the average RS-T elevation in a given lead.

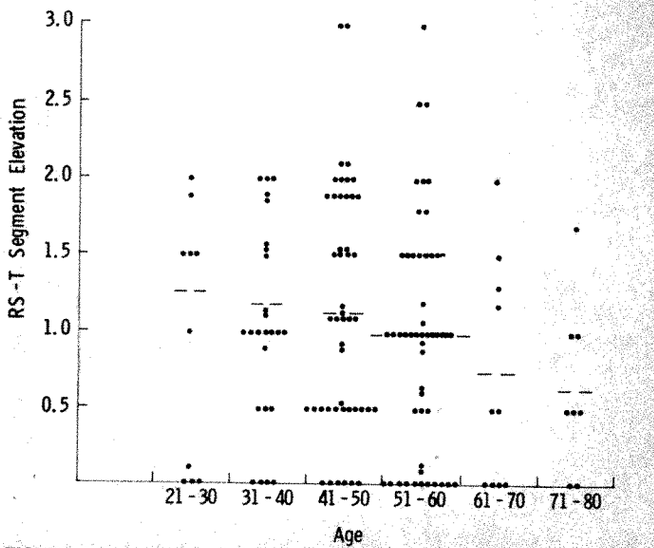

FIGURE 4. Correlation of RS-T segment elevation with age. All available electrocardiograms from 65 patients (total 525) were separated by age decades. When a patient had more than one electrocardiogram during the same age decade, the average height of the RS-T elevation (mm) in the available tracings was used. **Horizontal bars** indicate the mean for each age group.

TABLE I

Correlation of Greatest RS-T Segment Displacement in Precordial and Limb Leads in 65 Patients*

	Precordial Leads								
Limb Leads	0 mm	0.5 mm	1 mm	1.5 mm	2 mm	2.5 mm	3 mm	5 mm	Subtotal
0 mm	...	1	19	14	14	1		1	50 (77%)
0.5 mm	...	1	4	1	2	...	1		9 (14%)
1 mm	...	...	3	2	...	...	1		6 (9%)
Subtotal		2 (3%)	26 (40%)	17 (26%)	16 (25%)	1 (1.5%)	2 (3%)	1 (1.5%)	

* Data based on analysis of one electrocardiogram from each of the 65 patients showing the most typical changes of "early repolarization." The RS-T segment displacement was allocated to the nearest 0.5 mm and five patients with minimal elevation in limb leads were recorded as having 0 mm elevation.

tion," revealed that more than 90 percent of elevations were less than 2 mm in the precordial leads and less than 0.5 mm in the limb leads (Table I). Forty-five patients had no RS-T elevation in any limb lead, and no patient had RS-T elevation in the limb leads without precordial RS-T displacement.

Correlation of RS-T elevation with age (Fig. 4) revealed a general tendency to decreased RS-T displacement with increased age, but there was no statistical significance. Chronologic follow-up of RS-T elevation in each patient revealed no consistent pattern of evolution. In 17 (26 percent) of the 65 patients, RS–T elevation disappeared in at least one follow-up electrocardiogram; in 48 patients (74 percent) some RS-T elevation appeared in every recording (in 1 patient for 18 years [Fig. 5]), but the degree of elevation varied greatly from one recording to another.

J waves: Analysis of the electrocardiogram from each patient showing the most typical changes of early repolarization revealed that well developed or "embryonic" J waves were most frequently encountered in leads V_4 (32 patients), V_5 (23 patients) and V_3 (12 patients) but were uncommon in the limb leads (6 patients) (Table II). The height of the J waves was less than 3.5 mm. Distinct J points and slurred downstrokes of the QRS complexes were noted in the limb and precordial leads with about equal frequency (Table II). The three patterns of well defined or "embryonic" J wave, slurred downstroke and distinct J point varied from time to time in most patients (85 percent). Many electrocardiograms also showed more than one pattern in an individual tracing (83 percent) (Fig. 1).

QRS changes: Four patients had a "pseudo-R′" pattern in lead V_1 or V_2, or both (Fig. 6) that was similar

TABLE II

Pattern of Downstrokes of QRS Complexes in 65 Patients*

	J Wave and Pseudo-R′†	Slurred	Distinct J Point
Limb leads	6	47	31
Precordial leads	41	37	40

* Data based on analysis of one electrocardiogram from each of the 65 patients showing the most typical changes of "early repolarization."

† Four patients manifested "pseudo-R′" wave in lead V_1 or V_2.

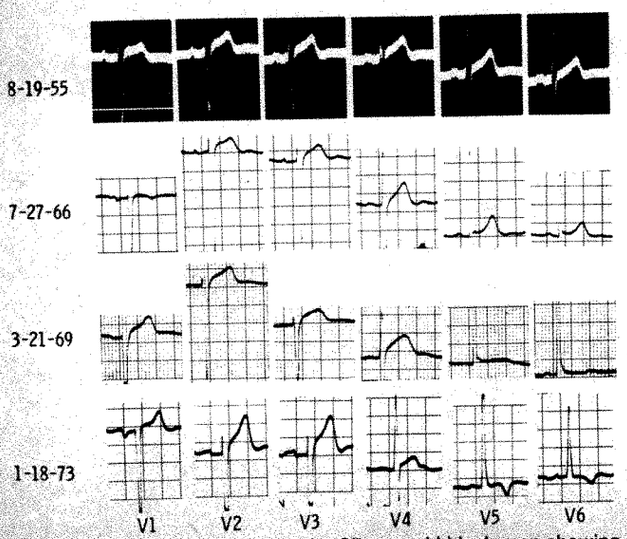

FIGURE 5. Electrocardiograms of a 37 year old black man showing sustained RS-T elevation in multiple tracings over a period of 18 years in spite of the development of left atrial overload and left ventricular hypertrophy because of hypertension.

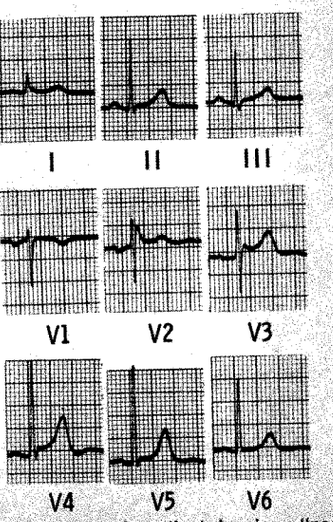

FIGURE 6. Electrocardiogram of a patient showing a "pseudo-R′" wave in leads V_2 and V_3. This patient was a 26 year old black man with sickle cell anemia who was admitted to the hospital because of vague chest pains and this electrocardiographic "abnormality."

to a pattern of incomplete or complete right bundle branch block. The transition of the QRS complex in the precordial leads (Fig. 7) showed a tendency to counterclockwise rotation. Electrocardiograms of 15 patients (23 percent) revealed a rapid change of QRS complexes in the transitional zone with an R/S amplitude ratio of less than 1:2 to greater than 2. In five patients (7.7 percent) the ratio was less than 1:3 to greater than 3 at the transition zone.

An R/S amplitude ratio of 1 or more in lead V_1 or V_2 was found in 1 and 5, respectively, of the 65 patients, a frequency that is similar to that found in asymptomatic subjects in a mass population study.[17] Forty-six patients had no clinical evidence of ventricular enlargement on physical examination and had normal heart size on chest roentgenogram. Among the remaining 19 patients, roentgenograms revealed mild to moderate cardiomegaly in 7 and were unavailable in 12. The average QRS voltage in lead V_6 in representative electrocardiograms of the 46 patients with known normal heart size was 1.7 mv (in 9 it was more than 2 mv). This value was significantly different ($P < 0.001$) from the average QRS voltage in lead V_6 of 1.35 mv in a normal asymptomatic age-matched population.

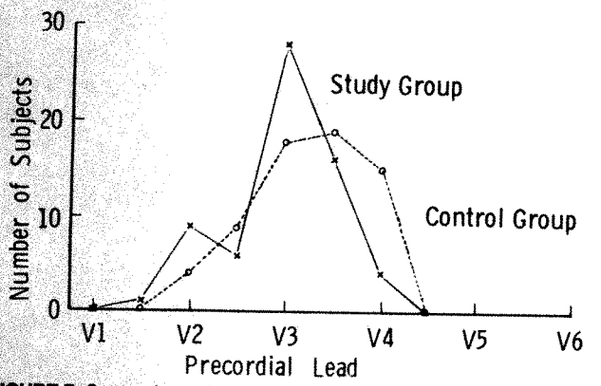

FIGURE 7. Comparison of the V lead QRS transitional zone in the study group (65 electrocardiograms with RS-T elevation) and in a control group (65 electrocardiograms without RS-T elevation). The control group was collected at random from numerous samples of electrocardiograms coded as "normal" without RS-T elevation. Patients in the control group were matched in age, sex and race with the study group. A statistically significant difference ($P < 0.025$) was found.

T and U waves: Evaluation of the height of T and U waves showed no characteristic change, and the amplitude of U waves was less than 2 mm in all instances. Six patients with RS-T segment elevation had prominent terminal T wave inversion in the mid- and left precordial leads consistent with the "labile T wave syndrome" (Fig. 8A). One patient had a "juvenile T wave pattern" (Fig. 8B) and another had "isolated T negativity" (Fig. 8C).

Discussion

The normal variant of RS-T segment elevation is a well recognized electrocardiographic finding.[1–5] It is seen in approximately 1 to 2.5 percent[6] of healthy adults and is more commonly encountered in young black patients[3,7–13] although some studies[4–16] have concluded that there is no racial variation. In our study, 52 of 65 patients (80 percent) were of black racial origin and this prevalence was out of proportion to the frequency of the black population in our general inpatient population, which has ranged from 40 to 53 percent over the years. The wide age range (22 to 80 years) has been found in previous studies.[18]

Characteristics of RS-T elevation: The physiologic basis for this normal variant is not well established, but it is considered a result of early onset of repolarization of the ventricle in a nonhomogeneous manner preceded by the epicardial surface vector,[19] and it may be associated with reciprocal RS-T depression in opposite leads. The RS-T elevation is most commonly encountered in leads V_2 to V_5 and is most prominent in lead V_3 or transitional areas because the S-T spatial vectors are relatively parallel with or slightly more anterior than the mean QRS and T vectors.[4] Because of this vector orientation, the repolarization vector often produces the most significant elevation in the precordial leads and is often associated with large T waves. RS-T elevation limited only to limb leads is uncommon,[6] and no cases were found in our study. The degree of elevation is usually less than 2 mm but may be greater in exceptional cases (Fig. 3). We found persistence of RS-T el-

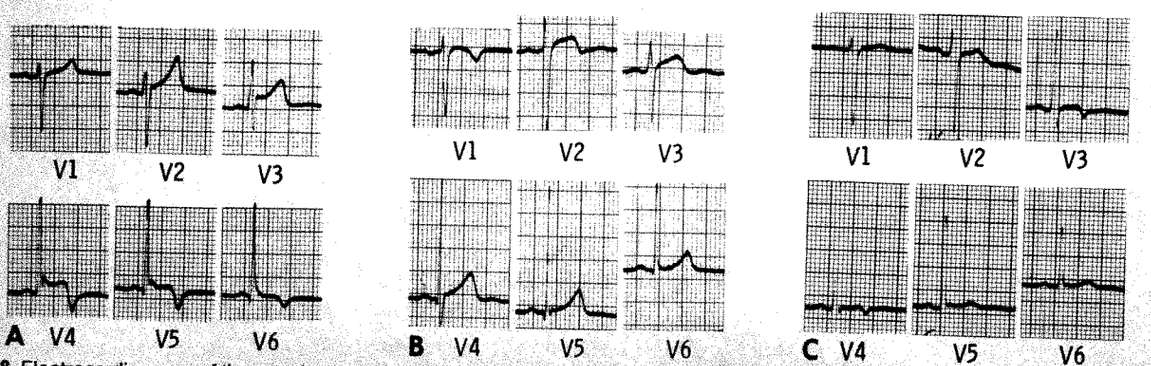

FIGURE 8. Electrocardiograms of three patients showing T wave changes. **A,** from a 60 year old black man with a "labile" T wave pattern as well as the early repolarization syndrome. He had no clinical evidence of heart disease. **B,** from a normal 42 year old black man with a "juvenile" T wave pattern (inverted T wave in leads V_1 and V_2). Also note the large QRS voltage in leads V_4 and V_5. **C,** from a normal 39 year old black man with "isolated T negativity" in leads V_3 and V_4. This is occasionally encountered in patients with early repolarization.

evation for decades in many patients (Fig. 5). RS-T segment displacement tended to decrease with increased age (Fig. 4); this tendency might be related to the normal aging process, myocardial ischemia, digitalis, other medications or electrolyte imbalance, but because of marked intraindividual variability of RS-T elevation, no statistically significant relations could be drawn.

QRS and J point features: The characteristics of the downstroke of the QRS complex were classified into three types: (1) well developed J waves and "embryonic" J waves, (2) slurred downstrokes, and (3) distinct J points. These three types may be seen in one electrocardiogram or may change from one type to another in subsequent electrocardiograms, but long-term follow-up study revealed no consistent pattern in any individual patient. This inconsistency could have been partly due to variations in the frequency response of various electrocardiographic machines. Four patients had "pseudo-R′" waves (Fig. 6) that mimicked incomplete or complete right bundle branch block; however, in these cases the terminal QRS vector was not directed to the right but anteriorly and slightly leftward in the horizontal plane. This "pseudo-R′" wave probably consists of a fusion of a terminal component of the QRS complex and the J wave. The patient whose tracing is shown in Figure 6 was admitted to the hospital for suspected pulmonary embolism because of chest pain and the "abnormal electrocardiogram."

A rapid QRS transition zone in the precordial leads was a common characteristic, and statistically significant precordial counterclockwise rotation[5] was noted ($P < 0.025$) in comparison with findings in a control group studied (Fig. 7). Increased QRS voltage mimicking left ventricular hypertrophy in the precordial leads (Fig. 2) was frequently encountered in subjects with no other evidence of ventricular enlargement but, in general, QRS voltage in lead I remained normal and the intrinsicoid deflection was not delayed. The characteristic of unusually tall T waves, often associated with this variant,[7] was not noted in our study. The greater age of our patients may explain this discrepancy.

Abnormal T wave patterns: Eight patients presented with various T wave changes known as "labile" T wave pattern (six patients, Fig. 8A), "juvenile" T wave pattern (one patient, Fig. 8B) and "isolated T wave negativity" syndrome (one patient, Fig. 8C). None of the eight had evidence of heart disease. These patterns sometimes closely mimic pericarditis or patterns of epicardial injury.[20] Many patients with this finding have elevated RS-T segments that return to the isoelectric line after exercise[3,21,22] or negative T waves that become upright after intravenous administration of potassium salts or propantheline bromide.[23] Whether these maneuvers are of significant diagnostic value in reliably separating "normal" from "abnormal" subjects remains to be established.

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Effect of Nitroglycerin Ointment on the Clinical and Hemodynamic Response to Exercise

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The effects of nitroglycerin ointment (15 mg nitroglycerin) on hemodynamics at rest and during exercise were studied in 12 patients with coronary artery disease and exertional angina (angina group) and in 8 patients with normal coronary arteriograms or with nonsignificant arteriographic abnormalities who did not have exertional chest pain (nonangina group). In both groups at rest nitroglycerin ointment induced within 15 minutes a significant decrease in left ventricular end-diastolic pressure that was sustained for at least 60 minutes; systemic arterial pressure also decreased within 15 minutes and continued to decrease during the 60 minutes of observation. By 30 to 60 minutes there were significant decreases in cardiac index, stroke index, left ventricular stroke work index and tension-time index.

During exercise performed 60 minutes after receiving nitroglycerin ointment, 10 of the 12 patients in the angina group had no pain, whereas 2 had delayed and less severe symptoms. Hemodynamic observations during this exercise period revealed significant decreases in left ventricular end-diastolic pressure, systemic pressure and tension-time index from values in the initial exercise period; heart rate remained unchanged. These data document the protective effect of nitroglycerin ointment for a period of at least 60 minutes and also suggest that the beneficial effects are related to a reduction in myocardial oxygen requirements.

Sublingually administered nitroglycerin is the most widely used drug in the symptomatic treatment of angina pectoris due to occlusive coronary artery disease. In addition to having a beneficial effect on symptoms, it is known to improve left ventricular performance and myocardial metabolism when administered before a stress such as exercise or pacing-induced tachycardia.[1,2] However, these effects are limited by its relatively short duration of action. Other nitrate drugs have been demonstrated to have a more prolonged period of action although considerable controversy exists as to the duration of action and efficacy of such long-acting nitrates.[3–10]

Nitroglycerin ointment has also been used for many years to treat angina pectoris. This preparation has been shown to improve exercise tolerance for up to 3 hours,[11,12] but no detailed information is available regarding its hemodynamic effects. This study was undertaken to assess the clinical and hemodynamic effects of nitroglycerin ointment at rest and during exercise in patients with coronary artery disease.

Methods

Hemodynamic investigations with subsequent selective coronary cinearteriography and left ventriculography were performed in 20 men with known or suspected coronary artery disease. The patients ranged in age from 28 to 62 years (average 47 years). Informed consent was obtained from each. None of the patients demonstrated cardiomegaly, arrhythmias or clinical evidence of cardiac failure and none were receiving digitalis, diuretic drugs or propranolol at the time of study.

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Protocol: The day before the study the patients were brought to the laboratory so that they would become familiar with the surroundings and the nature of the procedure. At this time they performed supine leg exercise on a bicycle ergometer so that we could observe their response to the stress and estimate the exercise load required to induce chest pain within 3 to 6 minutes.

Patients were studied in the fasting state and were given 100 mg of orally administered Nembutal® 45 minutes before coming to the hemodynamic laboratory. Under local anesthesia, the brachial artery and an accompanying vein were isolated in the right antecubital fossa. A no. 8 single lumen Cournand catheter was passed into the right side of the heart so that the tip lay in the pulmonary artery. A no. 8 Sones catheter was inserted into the left ventricle from the right brachial artery and the left brachial artery was cannulated with a Teflon® needle using the Seldinger technique. Lead II of the electrocardiogram and pressures from the pulmonary artery, brachial artery and left ventricle were recorded during a 15 minute control period. Cardiac output was measured in duplicate during the final 3 minutes with the dye-dilution technique using indocyanine green. Supine leg exercise was then carried out for 7 minutes while the electrocardiogram was continuously monitored and pressures were measured during the 1st, 3rd, 5th and 7th minutes. The cardiac output determination was repeated during the final 2 minutes of the exercise period.

Fifteen minutes after completion of the initial exercise period, hemodynamic measurements including cardiac output were made in all patients. Then approximately 3 cm of 2 percent nitroglycerin ointment (15 mg) was applied to an area of approximately 230 cm^2 on the anterior chest wall. The ointment was covered with a plastic wrap and left in place until completion of the second exercise period.

Hemodynamic observations at rest were carried out 15, 30, 45 and 60 minutes after application of nitroglycerin ointment. Following the hemodynamic observations at 60 minutes, a second period of exercise was carried out at the same work load used during the initial exercise period. Hemodynamic observations were made as during the initial exercise period.

Pressures were measured with P23DB Statham strain gauges from a zero reference level 5 cm below the angle of Louis and were recorded on a photographic recorder. Pressures were measured over at least two respiratory cycles, and the mean pressures in the brachial and pulmonary arteries were obtained electronically. Recording speed was normally 25 mm/sec but for determination of left ventricular diastolic pressure, a high sensitivity was employed with a speed of 100 mm/sec.

The left ventricular stroke work index in g-m/m^2 was calculated using the formula LVSWI = SI × (BAMP − LVEDP) × 13.6/1,000 where SI = stroke index in milliliters per square meter and BAMP = brachial arterial mean pressure and LVEDP = left ventricular end-diastolic pressure in millimeters of mercury. A modified tension-time index was calculated as the product of peak left ventricular systolic pressure and heart rate.

Coronary arteriography: Selective coronary cinearteriography and left ventriculography were then carried out in all 20 patients. Twelve patients were found to have occlusive coronary artery disease with greater than 75 percent obstruction in at least one coronary artery; 5 of the 12 had documented previous myocardial infarction. In these 12 patients left ventriculograms were normal in six and showed hypokinesia in 2 and focal or generalized hypokinesia in 4. Of the eight remaining patients, 5 had minimal irregularities in the coronary arterial tree but no significant obstructive lesions and 3 had normal coronary arteriograms.

Results

Each of the 12 patients with significant coronary artery disease experienced angina pectoris during the initial period of exercise (angina group). This developed within 2 to 6 minutes (average 3.4 minutes) and persisted until exercise was terminated. The five patients with minor coronary arteriographic irregularities and

TABLE I
Summary of Hemodynamic Effects of Supine Leg Exercise Before and After Nitroglycerin Ointment (mean ± standard error)

	BAMP (mm Hg)	LVEDP (mm Hg)	PAMP (mm Hg)	HR (beats/min)	CI (L/min/m^2)	SI (ml/m^2)	LVSWI (g-m/m^2)	TTI (mm Hg min × 10^{-1})	dP/dt (mm Hg sec)
A. Angina Group (no. = 12)									
Control	102 ± 4	11 ± 2	16 ± 1	72 ± 3	3.1 ± 0.1	44 ± 3	55 ± 5	947 ± 102	1803 ± 180
Exercise	127 ± 6	27 ± 2	35 ± 3	114 ± 6	5.1 ± 0.4	44 ± 4	59 ± 5	2054 ± 153	2520 ± 211
Recovery-15	103 ± 4	10 ± 2	16 ± 2	81 ± 3	3.2 ± 0.1	41 ± 2	51 ± 2	1135 ± 82	1700 ± 138
NGO-15	93 ± 4	6 ± 1	12 ± 2	80 ± 5	3.0 ± 0.1	40 ± 2	48 ± 3	986 ± 67	1705 ± 160
NGO-30	95 ± 4	6 ± 1	11 ± 2	81 ± 4	2.8 ± 0.1	37 ± 2	45 ± 4	1007 ± 77	1744 ± 110
NGO-60	85 ± 4	6 ± 1	13 ± 1	79 ± 3	2.9 ± 0.1	37 ± 3	39 ± 3	901 ± 50	1611 ± 265
Exercise-NGO	108 ± 4	12 ± 2	22 ± 3	115 ± 6	5.0 ± 0.2	44 ± 3	56 ± 3	1843 ± 151	2539 ± 299
B. Nonangina Group (no. = 8)									
Control	93 ± 3	8 ± 1	13 ± 2	77 ± 6	3.0 ± 0.3	40 ± 4	46 ± 3	976 ± 110	1548 ± 165
Exercise	114 ± 7	17 ± 2	25 ± 2	105 ± 4	5.1 ± 0.4	49 ± 4	64 ± 4	1709 ± 158	2310 ± 176
Recovery-15	94 ± 4	6 ± 1	12 ± 1	83 ± 4	3.1 ± 0.2	38 ± 3	44 ± 3	1041 ± 77	1606 ± 136
NGO-15	85 ± 4	4 ± 1	10 ± 1	84 ± 5	3.0 ± 0.3	37 ± 4	41 ± 5	882 ± 46	1583 ± 97
NGO-30	83 ± 2	3 ± 1	10 ± 1	87 ± 6	2.6 ± 0.3	30 ± 3	33 ± 4	965 ± 79	1613 ± 76
NGO-60	75 ± 2	5 ± 1	11 ± 1	84 ± 4	3.0 ± 0.2	36 ± 3	34 ± 2	834 ± 45	1427 ± 95
Exercise-NGO	94 ± 4	6 ± 1	16 ± 1	109 ± 6	4.8 ± 0.2	43 ± 3	52 ± 3	1496 ± 132	2270 ± 218

BAMP = brachial arterial mean pressure (mm Hg); CI = cardiac index (liters/min per m^2); dP/dt = first derivative of left ventricular systolic pressure curve (mm Hg·sec); Exercise-NGO = exercise 60 minutes after nitroglycerin ointment; HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVSWI = left ventricular stroke work index (g-m/m^2); NGO-15, NGO-30, NGO-60 = values at rest 15, 30 and 60 minutes, respectively, after nitroglycerin ointment; PAMP = pulmonary arterial mean pressure (mm Hg); Recovery-15 = 15 minutes after completion of initial exercise period; SI = stroke index (ml/m^2); TTI = modified tension-time index (mm Hg·min × 10^{-1}).

the three with normal arteriograms (nonangina group) did not experience pain during either exercise period. There were no complications during the study, but lightheadedness due to systemic hypotension developed in two patients between 50 and 60 minutes after administration of nitroglycerin. This symptom decreased after elevation of the legs and was not a problem as soon as the second exercise period was started.

Table I summarizes the hemodynamic data at rest and exercise before and after the administration of nitroglycerin and Table II shows the significance of change in the hemodynamic variables during the different phases of the study.

Angina Group (12 Patients) (Fig. 1 to 4)

During the initial exercise period the patients with angina manifested the abnormal hemodynamic response commonly seen during exertional angina. Left ventricular end-diastolic pressure increased to an average value of 27 mm Hg (P <0.001); there was no significant change in stroke index or left ventricular stroke work index. Sixty minutes after administration of nitroglycerin there were significant decreases from recovery levels in the resting values for brachial arterial mean pressure (P <0.01), left ventricular end-diastolic pressure (P <0.001), cardiac index (P <0.01), stroke index (P <0.05), left ventricular stroke work index (P <0.005) and tension-time index (P <0.02). Heart rate did not change significantly but was higher than the initial resting value (P <0.005). This finding may indicate that inadequate time was allowed before recovery data were obtained. A significant decrease in cardiac index (P <0.05) observed 30 minutes after administration of nitroglycerin persisted at 60 minutes. The decrease in left ventricular end-diastolic pressure was noted within 15 minutes of drug administration and remained relatively constant at that level. Brachial arterial mean pressure decreased within 15 minutes and continued to decrease over the hour. The response to exercise after nitroglycerin was quite normal. Comparison of hemodynamic data during exercise before and after administration of nitroglycerin demonstrated significant decreases in brachial arterial mean pressure (P <0.001), left ventricular end-diastolic pressure (P <0.001) and tension-time index (P <0.005) but no significant change in heart rate, cardiac index, stroke index or left ventricular stroke work index.

During the second exercise period, 10 of the 12 patients experienced no chest discomfort, and in 2 pain was delayed and less severe than during exercise before drug administration. Six patients had S-T segment depression of 2 mm or more during the initial exercise

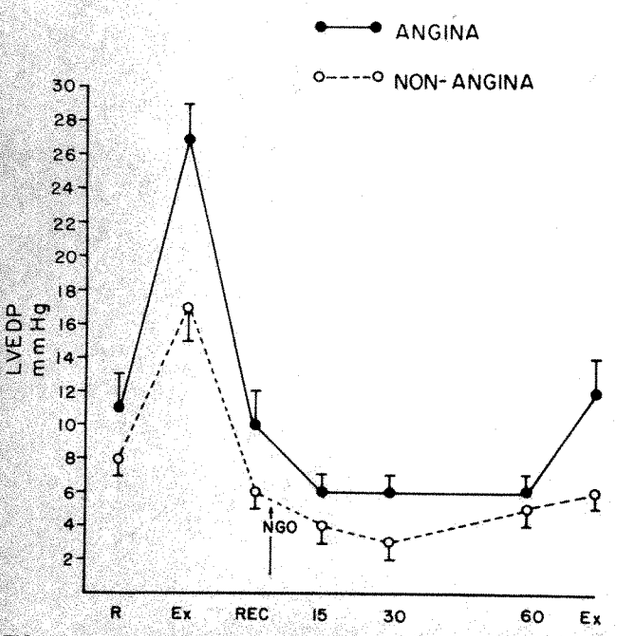

FIGURE 1. Left ventricular end-diastolic pressure (LVEDP) rose to abnormal levels during exertional angina. It was lowered 15 minutes after application of nitroglycerin ointment (NGO) and remained at this level until 60 minutes. During the second exercise period left ventricular end-diastolic pressure remained normal. Ex = exercise; R = rest; REC = recovery.

TABLE II

Summary of Significance of Changes (P Values) at Rest and During Exercise After Nitroglycerin Ointment

	Recovery Versus Exercise	Recovery Versus Nitroglycerin Ointment	Control Exercise Versus Exercise After Nitroglycerin Ointment
	Angina Group (no. = 12)		
BAMP	<0.001	<0.01	<0.001
LVEDP	<0.001	<0.001	<0.001
HR	<0.001	NS	NS
CI	<0.001	<0.01	NS
SI	NS	<0.05	NS
LVSWI	NS	<0.005	NS
TTI	<0.001	<0.02	<0.005
dP/dt	NS	NS	NS
	Nonangina Group (no. = 8)		
BAMP	<0.01	<0.001	<0.001
LVEDP	<0.01	<0.05	<0.001
HR	<0.001	NS	NS
CI	<0.001	NS	NS
SI	<0.005	NS	<0.01
LVSWI	<0.001	<0.01	<0.005
TTI	<0.001	<0.005	<0.05
dP/dt	<0.005	NS	NS

NS = not significant; other abbreviations as in Table I.

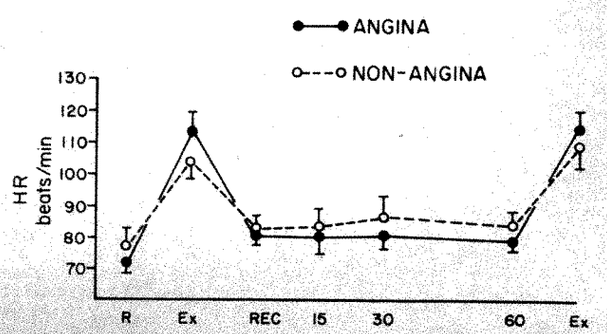

FIGURE 2. Heart rate (HR) during the two exercise periods was similar before and after application of nitroglycerin ointment.

period but only one of the six had such depression during the second exercise period. In this patient S-T segment depression decreased from 3 to 2 mm.

Nonangina Group (8 Patients) (Fig. 1 to 4)

The response to exercise in this group differed from the response of the angina group. The increases in left ventricular end-diastolic pressure and heart rate were less, and both stroke index and left ventricular stroke work index increased significantly. After nitroglycerin there were significant decreases in brachial arterial mean pressure, left ventricular end-diastolic pressure, left ventricular stroke work index and tension-time index. Cardiac index was significantly decreased by 30 minutes ($P < 0.025$) but was not significantly different from recovery values at 60 minutes. As with the angina group, heart rate showed no significant change compared with recovery data although there was a significant increase from initial resting values ($P < 0.02$). The response to exercise after nitroglycerin was normal. Comparison of the two exercise periods revealed significant decreases in brachial arterial mean pressure ($P < 0.001$), left ventricular end-diastolic pressure ($P < 0.001$), stroke index ($P < 0.01$), left ventricular stroke work index ($P < 0.005$) and tension-time index ($P < 0.05$); heart rate and cardiac index showed no significant change.

Discussion

Our study demonstrates that nitroglycerin ointment can produce rapid changes in hemodynamics that persist for at least 60 minutes. In patients with coronary artery disease these changes are associated with improved exercise tolerance and enhanced left ventricular performance.

The precise mechanism whereby nitroglycerin and other nitrates relieve angina pectoris remains unclear. With use of angiographic techniques, nitroglycerin has been shown to dilate coronary vessels. In normal subjects it increases coronary blood flow,[13] but its effect on coronary flow in patients with coronary artery disease is uncertain. It has been suggested that the beneficial effects of the nitrate drugs may be due to a redistribution of coronary blood flow rather than to an increase in total coronary flow.[14] However, there is considerable evidence that the beneficial effects are due to peripheral venous and arteriolar dilatation, which reduces ventricular preload, afterload and wall tension and, therefore, myocardial oxygen requirements.[2,15–19] The reduction in coronary perfusion pressure might be expected to have a deleterious effect on coronary blood flow, but the associated decrease in left ventricular diastolic pressure minimizes the change in transmyocardial pressure gradient.[19]

Hemodynamic responses to nitroglycerin ointment: The hemodynamic alterations induced by nitroglycerin ointment are similar to those seen with sublingually administered nitroglycerin but are delayed in onset and more prolonged. Within 15 minutes of application of the ointment, left ventricular filling pressure and systemic pressure were reduced. The change in filling pressures persisted throughout the study, whereas there was a progressive decrease in brachial arterial mean pressure.

These changes in left ventricular preload and afterload were similar in both groups of patients and represent the effects of nitroglycerin on venous capacitance vessels and peripheral arterioles. The cardiac index in the angina group was significantly reduced within 30 minutes of the application of nitroglycerin ointment and even at 60 minutes was significantly lower than during the control period. Similar changes in cardiac index were seen in the nonangina group although by 60 minutes the differences were not significant. The reduction in cardiac index possibly reflects the peripheral vasodilating effects of nitroglycerin in the presence of normal left ventricular filling pressures. In left ventricular failure, however, flow is maintained or increases as left ventricular filling pressures decrease with administration of nitroglycerin.[20,21] Thus, 60 minutes after nitroglycerin there was a decrease in brachial arterial mean pressure, tension-time index, left ventricular end-dia-

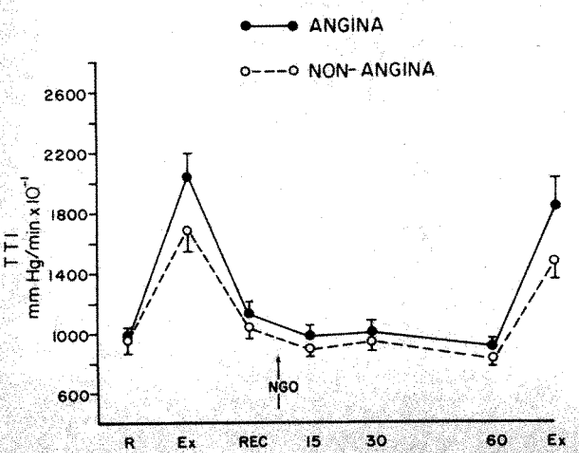

FIGURE 3. Tension-time index (TTI) was significantly lower during exercise in both the angina and nonangina groups after application of nitroglycerin ointment (NGO).

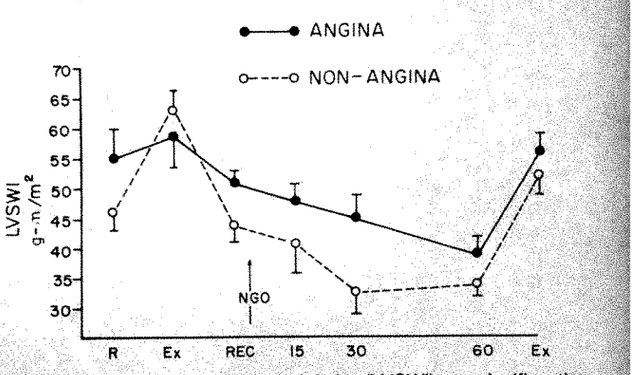

FIGURE 4. Left ventricular stroke work index (LVSWI) was significantly lower at rest after application of nitroglycerin ointment. During exercise it was lower after application of ointment in the nonangina group but did not change significantly in the patients with angina.

stolic pressure and presumably left ventricular end-diastolic volume, changes that would tend to diminish myocardial oxygen requirements.

During exercise, both groups of patients had hemodynamic alterations suggesting diminished left ventricular oxygen requirements after nitroglycerin. A primary determinant of oxygen requirements of the heart is the tension developed by the myocardium. The external index of tension as calculated by the tension-time index does not take into account the important influence of left ventricular volume in determining wall tension for any given pressure load. Thus, since left ventricular volume probably decreased after nitroglycerin, total wall tension decreased even more than indicated by the reduction in tension-time index.

Duration of action: The study protocol did not permit us to make observations on the duration of action of nitroglycerin ointment, but hemodynamic data are available to indicate persistence of these effects for as long as 4 hours.[20] Exercise capacity was improved 60 minutes after the application of nitroglycerin ointment. In a previous study[12] with nitroglycerin ointment increased exercise capacity was demonstrated 3 hours after drug administration. In our study, both exercise periods were of equal duration. The time of onset for angina during the initial exercise period averaged 3.4 minutes (range 2 to 6 minutes). It is possible that the 10 patients who remained free of pain after nitroglycerin would have been able to continue exercise for longer than the 7 minutes or to exercise at an increased work load.

The exact duration of action of the long-acting nitrate drugs is controversial. Sublingually administered isosorbide dinitrate has been shown to have beneficial effects within 5 minutes, but its duration of action is not clear. Different reports suggest that its beneficial clinical effects and hemodynamic alterations persist for 45 to 120 minutes.[3,6,7,10] Orally administered isosorbide dinitrate may have significant effects within 30 minutes of ingestion, and these effects may persist for up to 4.5 hours.[3] The continued absorption of nitroglycerin through the skin, which avoids early passage through the portal circulation, may be responsible for the prolonged effect of nitroglycerin when it is used in this fashion. We have no information about development of drug tolerance because none of our patients had previous exposure to this form of drug administration.

Clinical implications: Our results suggest that the administration of nitroglycerin in ointment form may be valuable in the prophylaxis of angina pectoris, and further investigation of this treatment is warranted. The sustained hemodynamic effects also suggest that this agent may be useful in the management of complicated acute myocardial infarction.[20]

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Association of Ostium Secundum Atrial Septal Defects With Mitral Valve Prolapse

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Severe prolapse of the mitral valve leaflets was seen at left ventricular angiography in 16 of 92 patients with a secundum type atrial septal defect studied prospectively from 1970 to 1974. The patients were aged 15 to 69 years; angioplasty or mitral valve replacement was carried out in nine. In 9 of 122 patients aged 15 to 55 years who were operated on for closure of a secundum type atrial septal defect between 1956 and 1969, mitral regurgitation due to prolapse but with intact chordae tendineae was seen at operation. In three of these patients chordal rupture was seen at a second operation 2 to 6 years later. The outlook in the syndrome of mitral valve prolapse may be less benign than is usually believed.

The mitral valve prolapse syndrome has been extensively studied in recent years. Initially in 1966,[1] and more frequently since 1970,[2–7] its frequent association with ostium secundum atrial septal defect has been pointed out. No explanation has been offered for this finding. We report here our data on the coexistence of these cardiac abnormalities.

Patients and Methods

The association of hemodynamically important mitral regurgitation in some adults with a secundum atrial septal defect prompted this study. The association of mitral valve prolapse with an atrial defect is found at all ages; however, to evaluate the ultimate incidence in the adult population, we excluded from this analysis the small children of our experience since prolapsing of the mitral valve may develop or progress with body growth. The case material consisted of a prospective and retrospective series:

1. All of 92 patients more than 15 years of age operated on for closure of a secundum atrial septal defect at the Texas Heart Institute after January 1970 underwent preoperative cardiac catheterization studies that included a left ventricular cineangiogram in either the posteroanterior or the left anterior oblique projection. At operation, the status of the mitral valve was assessed, with the aim of detecting any prolapse of the leaflets, dilatation of the anulus or elongation or rupture of the chordae tendineae. The preoperative clinical evaluation was also focused on possible coexistence of mitral valve prolapse with the secundum atrial septal defect.
2. The records of all 281 patients more than 15 years of age operated on for closure of a secundum atrial septal defect between 1956 and December 1969 were studied for evidence of abnormalities of the mitral valve suggestive of the mitral valve prolapse syndrome. Primary emphasis was given to the surgeon's observation of the mitral valve at operation.

Results

Prospective Series

Ninety-two of 269 patients who had closure of a secundum atrial septal defect between January 1970 and June 1974 were more than 15 years old; 38 were aged 15 to 35 years (Group A) and 54 were aged 35 to 69 years (Group B). Sixteen patients, 4 in Group A (10.5 percent) and 12 in Group B (22 percent), had angiographic (Fig. 1) or clinical evidence of the pro-

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lapsing mitral valve syndrome. Nine of the 92 (10 percent) required surgery for mitral regurgitation.

Clinical examination: The typical auscultatory findings of an atrial septal defect were present in all patients of both groups with the prolapsing mitral valve syndrome. In one patient in each group, there were no associated auscultatory findings of mitral valve abnormality. In all four Group A patients significant mitral regurgitation was associated with a holosystolic murmur of variable intensity at the sternal border. In two Group B patients the existence of mitral regurgitation or prolapse of the mitral valve was not suspected before cardiac catheterization. A midsystolic click was heard in only two Group B patients, one of whom had a late systolic and the other a holosystolic murmur. One additional patient in Group B had a late systolic murmur. Only 3 of the 16 patients in the prospective group had a nonejection click, but the majority had either a late or holosystolic murmur.

Electrocardiogram: All but two Group B patients had a frontal plane QRS axis between +50° and +110°. These two patients, aged 69 and 61 years, respectively, had an axis of −20° and −30°.

Surgical findings: Eleven patients had a sizable atrial septal defect corresponding to the location of an ostium secundum (diameter ± 3.0 cm). In all 11 a "floppy" mitral valve was seen.

Surgical results: In three Group A and three Group B patients annuloplasty was successfully performed. Three Group B patients had mitral valve replacement, and one of these, the only patient in the series who died, died suddenly 2 months postoperatively, probably from valve thrombosis.

Retrospective Series

Between 1956 and December 1969, a total of 702 patients had surgical closure of a secundum atrial septal defect. Of these, 122 were aged 15 to 35 years (Group A) and 159 aged 35 to 69 years (Group B). An abnormal mitral valve, in retrospect consistent with the prolapsed mitral valve syndrome, was described at surgery in nine patients, two in Group A (1.6 percent) and seven in Group B (4.4 percent). In all, a holosystolic murmur had been described. No patient was recorded as having a nonejection click. Two patients had atrial fibrillation and one a nodal rhythm. The surgical findings and natural history of these nine patients are interesting.

Group A (age 15 to 35 years): One of the two patients in this group had mitral valve replacement at the time of the closure of the atrial septal defect. The second had a mitral valve annuloplasty in 1966, with an initially good result. At that time the chordae tendineae were not ruptured. However, severe mitral insufficiency became evident in 1969, and he had a mitral valve replacement in 1972. At this time rupture of the posterior chordae was seen.

Group B (age 35 to 69 years): In four of the seven patients in this group the mitral insufficiency was not corrected at the time of the initial operation. Three of the four were operated on before 1963, when no acceptable mitral valve prosthesis was available. One of them died 17 days postoperatively with congestive heart failure. One has persistent moderate mitral regurgitation but is not yet considered a candidate for valve replacement. A third patient had closure of the atrial septal defect in 1967; chordal rupture was not found. By 1969, mitral regurgitation was clinically judged to be severe. At mitral valve replacement in 1973, a rupture of the posterior chordae tendineae was seen. The fourth patient had closure of the atrial septal defect in 1962. Mitral regurgitation was evident but judged to be mild, and the chordae tendineae were intact. Three years later bacterial endocarditis developed with the onset of severe mitral insufficiency. At mitral valve replacement in 1966 ruptured warty-appearing chordae tendineae were seen. The patient died on the 5th postoperative day.

In three Group B patients annuloplasty was performed simultaneously with closure of the atrial septal defect. One patient had an Ivalon® patch reconstruction for mitral re-

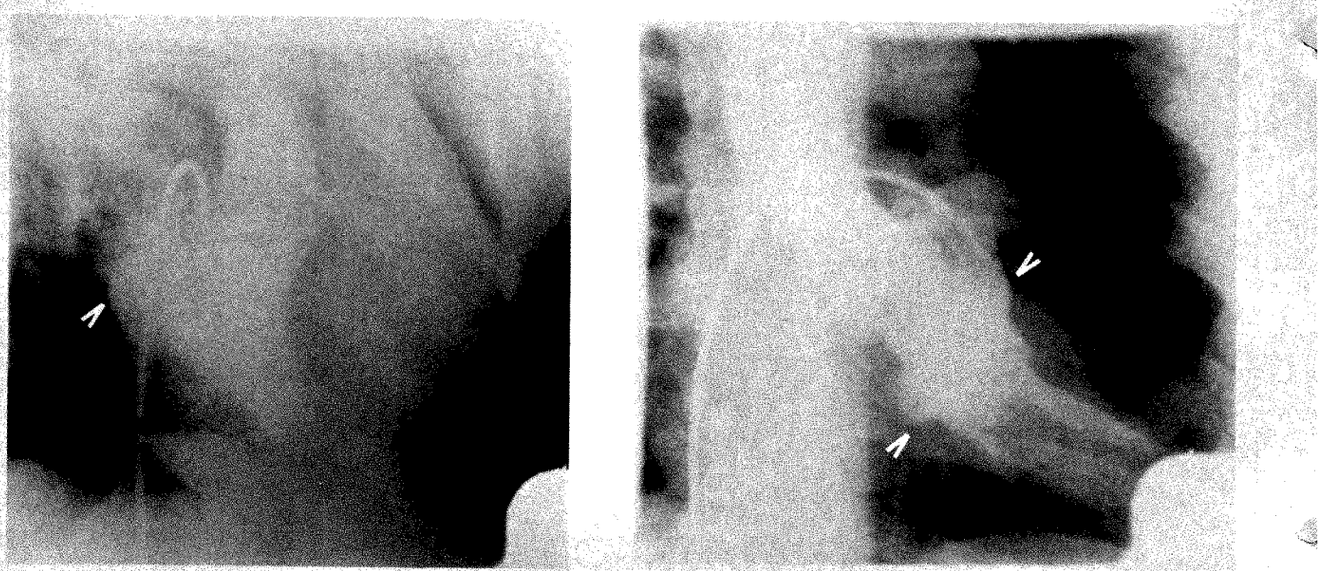

FIGURE 1. Left ventricular cineangiograms in the right anterior oblique **(left)** and anteroposterior projections **(right)**. The prolapse at the posterior leaflet and associated mitral insufficiency are well seen in the right anterior oblique view, and the dilated anulus of the mitral valve, confirmed at surgery, is seen in the anteroposterior view.

gurgitation in 1960 and died on the 1st postoperative day. Another patient had an annuloplasty performed in 1962. She remains well to date, with evidence of only minimal mitral regurgitation. A third patient had an annuloplasty in 1963, with findings of leaflet prolapse and anulus dilatation, but no chordal rupture. Because of increasing mitral insufficiency, replacement of the mitral valve was performed in 1965. At that time, it was observed that the annuloplasty had broken down and that the posterior chordae tendineae were ruptured. She died on the 1st postoperative day.

Histologic Examination

In one patient from the prospective series and in the five from the retrospective series, histologic examination of the excised mitral valve revealed myxomatous degeneration, said to be characteristic of the prolapsing mitral valve syndrome.[8]

Discussion

Our findings are generally in agreement with previous data. Others[2,5] have noted that a pansystolic murmur is more frequent than a late systolic murmur when mitral valve prolapse is associated with a secundum atrial septal defect and that midsystolic clicks are infrequent. There is no good explanation for these observations or for the prominence of the click after closure of the defect. Victorica et al.[4] noted that the click became more distinct in two patients after operation. It is our undocumented impression that at least 30 percent of patients operated or for closure of a secundum atrial defect will have a postoperative midsystolic click.

Betriu et al.[5] described some patients whose prolapsed mitral valve was diagnosed only at angiography, and we had two such patients whose clinical evaluation revealed only a secundum atrial defect.

Left axis deviation, an unusual electrocardiographic finding in uncomplicated secundum atrial defect, has been noted in some cases with mitral valve involvement due to the prolapsed mitral valve.[4,5] As stressed by Jeresaty,[6] care should be taken in such cases to exclude an ostium primum defect.

We noted an incidence rate of significant prolapsed mitral valve in 17 percent of our patients over 35 years of age with secundum atrial defect studied prospectively with the coexistence of these two defects in mind. The incidence rate was lower in younger patients (10.5 percent) and in our experience, although not analyzed in this review, it is even lower in small children.

Natural history: We think that the natural history of our patients initially operated on before 1969 offers some valuable new insight into the natural history of the prolapsing valve syndrome. This syndrome is generally considered benign,[9] but progression of the mitral apparatus malfunction has been seen, and bacterial endocarditis is known to occur.[10] Such progressive mitral valve deterioration was noted in four of our patients, in whom we were able to inspect the valve twice, at intervals of 2 to 6 years. In all four patients chordal rupture occurred between the first and second operation, in one case possibly because of intervening bacterial endocarditis. These observations lend further support to our belief[11] that mitral valve prolapse leads to mitral regurgitation and chordal rupture more frequently than is appreciated and that it is responsible for the greatest percentage of nonrheumatic acquired mitral regurgitation cases seen in adults.

Treatment: The increased number of older patients with clinically important mitral regurgitation in association with secundum atrial defect suggests that the course of patients with atrial septal defect may not be entirely benign after surgical treatment. Certainly those who have a midsystolic click postoperatively are candidates for potential further difficulty with the mitral valve. These patients should be evaluated periodically since some of them may require further surgical treatment of the mitral valve. Children who have had successful surgical closure of a secundum atrial defect should be observed for the presence of a midsystolic click at least until they attain adult stature. If there is evidence of mitral prolapse, perhaps antibiotic agents should be given during periods of risk as prophylaxis against bacterial endocarditis.

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Ventricular Monophasic Action Potential Changes Associated With Neurogenic T Wave Abnormalities and Isoproterenol Administration in Dogs

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Changes in the duration of monophasic action potentials on the anterior and posterior walls of the dog ventricle were correlated with changes in T wave polarity and duration of the Q-T interval after (1) left stellate ganglion transection, (2) right stellate ganglion stimulation, and (3) administration of isoproterenol before or after these procedures. Left stellate ganglion transection and right stellate ganglion stimulation produced similar changes in T wave polarity, but the former prolonged and the latter shortened the Q-T interval. All procedures changed the duration of the monophasic action potential and the Q-T interval in the same direction. The reversal of T wave polarity induced by left stellate ganglion transection, right stellate ganglion stimulation or administration of isoproterenol after left stellate ganglion transection was associated with an average change of 13 to 17 msec in the difference between the monophasic action potential durations on the anterior and posterior ventricular walls.

Isoproterenol restored to normal the neurogenic T wave abnormalities produced by left stellate ganglion transection and right stellate ganglion stimulation. The drug shortened the previously prolonged monophasic action potential more than the normal monophasic action potential, and the normal monophasic action potential more than the previously shortened monophasic action potential. This study confirms that the T wave is a sensitive indicator of relatively small changes (less than 20 msec) in the sequence of ventricular repolarization and explains the mechanism by which isoproterenol "normalizes" the primary T wave abnormalities.

Neurogenic abnormalities of ventricular repolarization in man have been known for more than 2 decades.[1,2] However, there is still no agreement concerning the mechanism and the clinical significance of these abnormalities.[3] In the dog, conspicuous T wave abnormalities can be produced by stimulation[4,5] or ablation[5] of the stellate ganglia and by stimulation of sympathetic nerve branches.[6] Yanowitz et al.[5] and Kralios et al.[6] have shown that these neurogenic abnormalities are associated with localized changes in the duration of the functional refractory periods of the ventricular myocardium. These changes have been attributed to localized changes in the duration of individual ventricular action potentials,[5] but the validity of this assumption has not yet been experimentally documented.

In our clinical studies[7] neurogenic T wave abnormalities could be transiently abolished by small doses of isoproterenol administered intravenously. However, the effect of isoproterenol was not limited to patients with central nervous system diseases. Isoproterenol "normalized" all primary T wave abnormalities except those attributed to myocardial ischemia and pericarditis. We have assumed that this effect of isoproterenol is caused by localized shortening of ventricular action potentials but have not verified this experimentally.

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It is technically difficult to record transmembrane action potentials with glass microelectrodes from a beating heart in situ. However, monophasic action potentials recorded with suction electrodes faithfully reflect the shape and duration of transmembrane action potentials.[8] In our previous studies we utilized the technique of monophasic action potential recording in dogs to study the sequence of ventricular repolarization[9] and the specificity and sensitivity of primary T wave abnormalities.[10] In this study we report correlations before and after administration of isoproterenol between the monophasic action potential and T wave changes in dogs with neurogenic T wave abnormalities. Our results support the assumption that neurogenic T wave abnormalities are associated with regional changes in duration of the monophasic action potential[5] and explain the mechanism of T wave "normalization" produced by administration of isoproterenol.[7]

Methods

Mongrel dogs weighing 11 to 18 kg were anesthetized with intravenously administered sodium pentobarbital (30 mg/kg body weight) and ventilated with a Harvard respirator. The chest was opened with a midsternal incision. A bipolar stimulating nichrome wire (diameter 0.06 mm) electrode (Driver Harrison Co.) was attached to the right stellate ganglion. The heart was suspended in a pericardial cradle. The sinoatrial node was crushed, and a bipolar Grass E2B platinum electrode was attached to the right or left atrium. The atria were paced with a Medtronic pacemaker (model 5800) at the slowest rate required to overdrive the spontaneous rhythm (range 120 to 150 beats/min). Another bipolar electrode was sutured to the surface of the right ventricle for ventricular pacing. The cardiac surface was covered with sponges soaked in warm saline solution. These sponges were replaced before each recording. The cardiac surface was heated by means of two model L510 explosion-proof surgical lamps (Wilmont Castle Co., Rochester, N.Y.), as described previously.[9] The temperature on the cardiac surface in individual experiments ranged from 34° to 37° C, but the difference in temperature between different recording sites in each experiment was less than 1° C.

Electrocardiographic recordings: We recorded simultaneously three orthogonal X, Y and Z electrocardiographic leads of the system designed for the dog by McFee and Parungao,[11] and two monophasic action potentials from the epicardial surface of the ventricular myocardium with a Hewlett-Packard multichannel direct-writing recorder on paper moving 100 mm/sec. Ventricular monophasic action potentials were recorded with bipolar suction electrodes, as described previously.[9] They were acceptable if (1) the amplitude exceeded 25 mv, (2) the course of repolarization was smooth, (3) atrial and ventricular pacing produced identical tracings,[9] and (4) 10 or more consecutive monophasic action potentials were identical. One monophasic action potential was recorded from the anterior surface of the left ventricle in the region containing test points 9, 11 and 13 in the dogs studied by Yanowitz et al. (Fig. 6 of Reference 5). This region was chosen because it was the site of the greatest changes in functional refractory periods after right stellate ganglionectomy.[5] Another monophasic action potential was recorded from the posterior surface of the left ventricle in the region containing test points 10 and 11 in the dogs studied by Yanowitz et al. (Fig. 7 of Reference 5). The method of measuring the duration of the monophasic action potential and the slope of phase 3 has been described previously.[8] These measurements were accurate within 5 msec.[9,10] The difference between the durations of simultaneously recorded monophasic action potentials on the anterior (A) and posterior (P) walls is designated Δ(A-P). A positive sign indicates that the monophasic action potential on the anterior wall was longer than that on the posterior wall. The Q-T interval designates the longest interval in simultaneously recorded X, Y and Z leads.

Stellate ganglion stimulation or transection: In some experiments we excised the left stellate ganglion and the upper thoracic sympathetic chain (T1 to T5). The right stellate ganglion was stimulated with a Grass S-4 stimulator for 30 seconds with a train of pulses with an amplitude of 10 to 15 volts, a duration of 2 msec and a frequency of 10 hertz. Because of stimulation artifacts, no satisfactory electrocardiograms and monophasic action potentials could be recorded during the stimulation. The electrocardiogram and the monophasic action potentials were recorded immediately after the end of the stimulation and every 30 seconds thereafter for 5 minutes.

Isoproterenol administration: Isoproterenol was administered in a 5 percent aqueous dextrose solution (1 μg/ml) by rapid hand injection into the main pulmonary artery through a 23 gauge hypodermic needle in doses of 2 to 6 μg. Electrocardiograms and monophasic action potentials were recorded every 30 seconds for 5 minutes after the injection. In each experiment the dose of isoproterenol was chosen in preliminary trial by gradually increasing the test doses to achieve greater than 5 msec shortening of the monophasic action potential without accelerating the heart rate above the rate of pacing and without inducing ventricular arrhythmia. This dose was kept constant in each dog during all procedures except for several experiments after stellate ganglion transection (see Results).

In most experiments, isoproterenol was administered both before and after stimulation or transection of the stellate ganglion. In each experiment the monophasic action potential was recorded from the same site before and after administration of isoproterenol. The potentials before and after right stellate stimulation were also recorded from the same site. However, the recording site after left stellate ganglion transection was usually changed because the amplitude of the monophasic action potential recorded before the transection tended to decrease during the 20 to 30 minute period required to complete the transection. Whenever it was necessary to change the site of application of suction, the new site selected was within a few mm of the old site.

The paired Student's t test was used to evaluate the statistical significance of the results. A value of $P < 0.01$ was considered significant.

Results

Control Experiments

The electrocardiograms and the monophasic action potential recordings resembled the records described in previous studies.[5,9,10,12] The T wave in the Y lead was positive and notched, or biphasic, that is, positive-negative (Fig. 1 to 3). The average duration of the monophasic action potential on the anterior surface was significantly longer than on the posterior surface (Tables I and II).

Isoproterenol, administered to nine dogs (10 experiments), produced effects similar to those described previously.[10] Figure 1 shows typical changes within 1 minute after the administration of 3 μg of isoproterenol. The QRS complex did not change whereas the Q-T in-

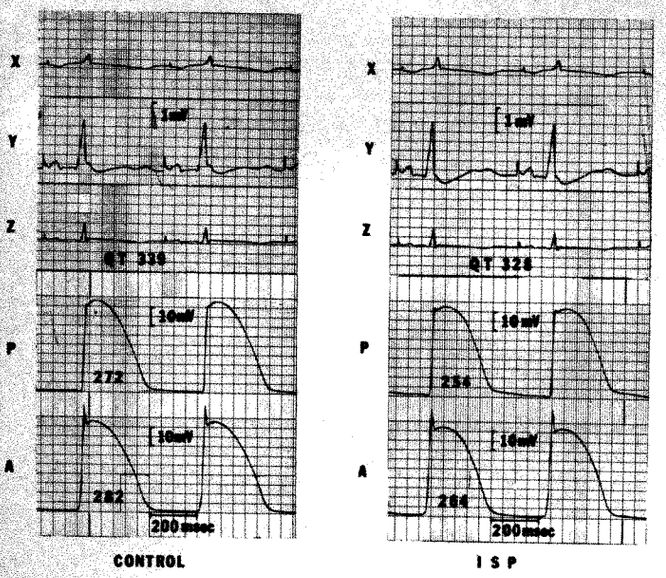

FIGURE 1. Effect of 3 μg of isoproterenol (ISP) infusion on the electrocardiogram and monophasic action potentials on the anterior (A) and posterior (P) walls of the left ventricle. The numbers show the durations of the monophasic action potentials and Q-T interval in msec. See text. Tracings retouched for clarity.

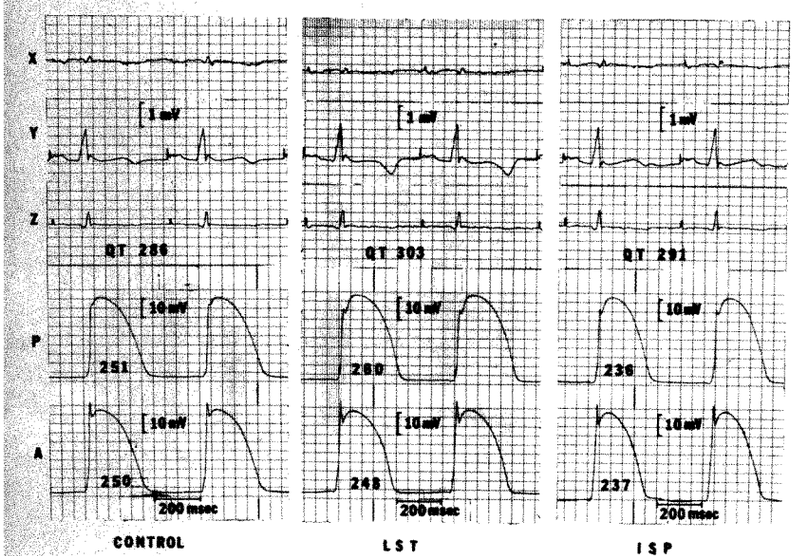

FIGURE 2. Effect of left stellate ganglion transection (LST) on the electrocardiogram and monophasic action potentials. Isoproterenol (3 μg) was administered after the transection. See text. Tracings retouched for clarity. Abbreviations as in Figure 1.

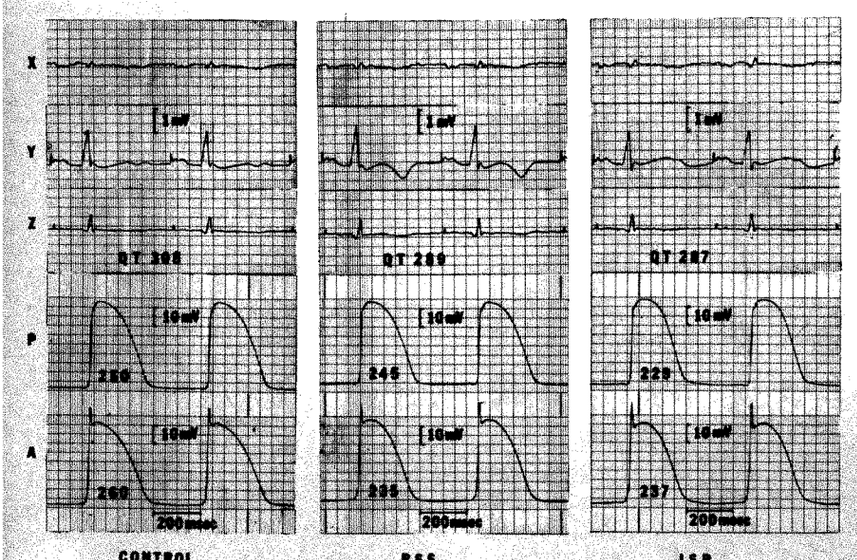

FIGURE 3. Effect of right stellate ganglion stimulation (RSS) on the electrocardiogram and monophasic action potentials. Isoproterenol (3 μg) was administered immediately after the termination of stimulation. See text. Tracings retouched for clarity. Abbreviations as in Figure 1.

terval and both monophasic action potentials shortened. In the Y lead, the S-T segment became depressed and T wave amplitude increased. Before admininstration of isoproterenol the terminal portion of the T wave in the Y lead was positive in seven dogs and negative in two. Isoproterenol either increased the amplitude of the positive T wave (Fig. 1) or reversed the polarity of a negative T wave. Table I shows that isoproterenol (3 to 5 μg) shortened the anterior monophasic action potential duration slightly more than the posterior but Δ(A-P) after isoproterenol was not significantly different from the control value. Isoproterenol shortened the Q-T interval but did not significantly change the slope of phase 3 of the monophasic action potential.

Left Stellate Ganglion Transection

The effect of left stellate ganglion transection was studied in eight dogs (Table II). In a typical experiment (Fig. 2) after left stellate ganglion transection the QRS complex did not change, the Q-T interval became longer, the duration of the P-R interval increased from 125 to 135 msec, and the diphasic T wave in the Y lead became deeply negative; left stellate ganglion transection also prolonged the monophasic action potential on the posterior wall but had a negligible effect on that on the anterior wall. Similar effects on the T wave and monophasic action potential were observed in other experiments. In one dog the amplitude of the positive T wave decreased, and in seven dogs the T wave became deeply negative. These T wave changes persisted, usually for several hours, until the dog was killed. A summary of the experiments (Table II) indicates that left stellate ganglion transection caused significant lengthening of the monophasic action potential on the posterior wall (P), had no significant effect on the anterior monophasic action potential (A), and reversed Δ(A-P) from plus to minus. The effect on the slope of phase 3 could not be measured accurately because of the decrease in amplitude of the monophasic action potential during the period required to complete the left stellate ganglion transection. Left stellate ganglion transection increased the average duration of the P-R interval by 10 ± 7 msec (mean ± standard deviation) ($P < 0.005$).

The effect of isoproterenol after left stellate ganglion transection was studied in eight dogs (Fig. 2, Table III). In four of these animals the rate of pacing was increased by 5 to 20 beats/min before administration of isopro-

TABLE I

Effect of Isoproterenol on Monophasic Action Potential Durations on the Anterior and Posterior Walls and on the Q-T Interval in Nine Dogs (10 Experiments)

	Before ISP (msec)	After ISP (msec)	Net ISP Effect (msec)
MAP-A	256 ± 22	235 ± 22	−21 ± 7†
MAP-P	241 ± 24	223 ± 21	−19 ± 5†
Δ(A-P)	+15 ± 9*	+12 ± 9**	−3 ± 5
Q-T	300 ± 25	284 ± 26	−15 ± 4†

Values expressed as mean ± standard deviation.

Δ(A-P) = difference between durations of simultaneously recorded monophasic action potentials on the anterior and posterior left ventricular walls; ISP = isoproterenol; MAP-A and MAP-P = monophasic action potential on, respectively, the anterior and posterior surface. The statistical significance of differences between MAP-A and MAP-P in the vertical columns is marked by asterisks, and between values in the horizontal columns by daggers; *, † = $P < 0.001$; ** = $P < 0.005$.

TABLE II

Effect of Left Stellate Ganglion Transection on Monophasic Action Potential Durations on the Anterior (A) and Posterior (P) Walls and on the Q-T Interval in Eight Dogs (Eight Experiments)

	Before LST (msec)	After LST (msec)	Net LST Effect (msec)
MAP-A	268 ± 44	269 ± 43	+1 ± 5
MAP-P	260 ± 45	274 ± 45	+14 ± 4†
Δ(A-P)	+8 ± 6*	−5 ± 8	−13 ± 3†
Q-T	295 ± 47	312 ± 45	+17 ± 5†

Values expressed as mean ± standard deviation.

LST = left stellate transection; other abbreviations as in Table I. The statistical significance of differences between MAP-A and MAP-P in the vertical columns is marked by asterisks, and between values in the horizontal columns by daggers; † = $P < 0.001$; * = $P < 0.01$.

TABLE III

Effect of Isoproterenol After Left Stellate Transection on Durations of Monophasic Action Potential on the Anterior (A) and Posterior (P) Walls and on the Q-T Interval in Eight Dogs (Nine Experiments)

	After LST Before ISP (msec)	After ISP (msec)	Net ISP Effect (msec)
MAP-A	256 ± 22	240 ± 21	−16 ± 5†
MAP-P	260 ± 20	230 ± 17	−29 ± 8†
Δ(A-P)	−4 ± 6	+10 ± 9*	+14 ± 9†
QT	299 ± 21	278 ± 24	−19 ± 8‡

Values expressed as mean ± standard deviation.

Abbreviations as in Tables I and II. The statistical significance of differences between MAP-A and MAP-P in the vertical columns is marked by asterisks, and between values in the horizontal columns by daggers; *, † = $P < 0.001$; ‡ = $P < 0.005$.

TABLE IV

Effect of Right Stellate Ganglion Stimulation on Monophasic Action Potential Durations on the Anterior (A) and Posterior (P) Walls, and on the Q-T Interval in Eight Dogs (16 Experiments)

	Before RSS (msec)	After RSS (msec)	Net RSS Effect (msec)
MAP-A	245 ± 24	222 ± 22	−24 ± 7†
MAP-P	232 ± 22	226 ± 22	−6 ± 3†
Δ(A-P)	+13 ± 8*	−4 ± 6	−17 ± 6†
QT	287 ± 18	273 ± 18	−14 ± 7†

Values expressed as mean ± standard deviation.

RSS = right stellate ganglion stimulation; other abbreviations as in Table I. The statistical significance of differences between MAP-A and MAP-P in the vertical columns is marked by asterisks, and between values in the horizontal columns by daggers; *, † = $P < 0.001$.

terenol. Figure 2 shows that isoproterenol restored the shape and polarity of the T wave to the control level, shortened the Q-T interval and shortened monophasic action potentials on both the anterior and posterior walls. The shortening was greater on the posterior than on the anterior wall, and Δ(A-P) became more similar to the control value. Table III shows that isoproterenol changed Δ(A-P) from −4 ± 6 to +10 ± 9 msec. The latter value was not significantly different from control Δ(A-P) in Tables I, II and IV.

Right Stellate Ganglion Stimulation

Typical effects of right stellate ganglion stimulation are shown in Figure 3; the QRS complex did not change, the P-R interval decreased from 124 to 110 msec, the Q-T interval shortened, the T wave became deeply negative in the Y lead and both monophasic action potentials shortened, but the shortening effect was greater on the anterior than on the posterior wall. Similar effects occurred in other experiments (Table IV). Right stellate ganglion stimulation reversed Δ(A-P) from plus to minus. This effect on Δ(A-P) was similar to the effect of left stellate ganglion transection (Table II). Right stellate ganglion stimulation shortened the average P-R interval by 13 ± 4 msec ($P<0.001$), and did not change significantly the slope of phase 3 of the monophasic action potential.

The effect of isoproterenol on the monophasic action potential and T wave changes induced by right stellate ganglion stimulation was studied in eight dogs (16 experiments). Figure 4 shows the method used to estimate the effect of isoproterenol on the course of spontaneous recovery after termination of right stellate ganglion stimulation in one of these experiments. Before right stellate ganglion stimulation, the anterior wall monophasic action potential was 14 msec longer than the posterior wall potential. Thirty seconds after the end of right stellate ganglion stimulation (arrow in Fig. 4A), the monophasic action potential shortened more on the anterior than on the posterior wall, and therefore the latter potential became 10 msec longer than the former. However, 90 seconds later the effect of right stellate ganglion stimulation dissipated and the anterior monophasic action potential was again longer than the posterior potential. Figure 4B shows the course of recovery in the same dog, when isoproterenol was administered after termination of right stellate ganglion stimulation. Figure 4C compares the time course of Δ(A-P) after right stellate ganglion stimulation alone and after right stellate ganglion stimulation plus isoproterenol. It can be seen that isoproterenol decreased the right stellate ganglion stimulation-induced Δ(A-P),

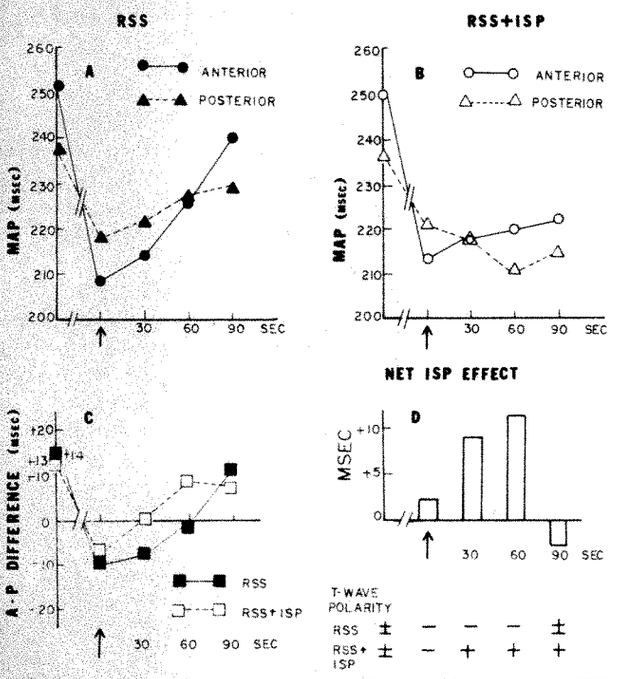

FIGURE 4. Method of estimating the contribution of isoproterenol (ISP) to the change in durations of the monophasic action potentials on the anterior (A) and posterior (B) walls after right stellate ganglion stimulation (RSS). **A,** time course after right stellate ganglion stimulation alone. **B,** after right stellate ganglion stimulation followed by administration of isoproterenol. On the ordinate, duration of the monophasic action potential in milliseconds and on the abscissa, time in seconds. The **arrows** in **A** and **B** mark 30 seconds after the end of right stellate ganglion stimulation. In **B,** the same **arrow** also marks the onset of administration of isoprotenerol. **C,** comparison of Δ(A-P) after right stellate ganglion stimulation alone (**A**) and right stellate ganglion stimulation plus isoproterenol (**B**). On the ordinate, Δ(A-P); on the abscissa, the same time sequence as in **A** and **B. D,** net effects of isoproterenol on the difference between the durations of simultaneously recorded monophasic action potentials on the anterior and posterior walls (Δ[A-P]) and T wave polarity in the Y lead after right stellate ganglion stimulation alone and right stellate ganglion stimulation followed by isoproterenol. + = positive; − = negative; ± = diphasic. See text.

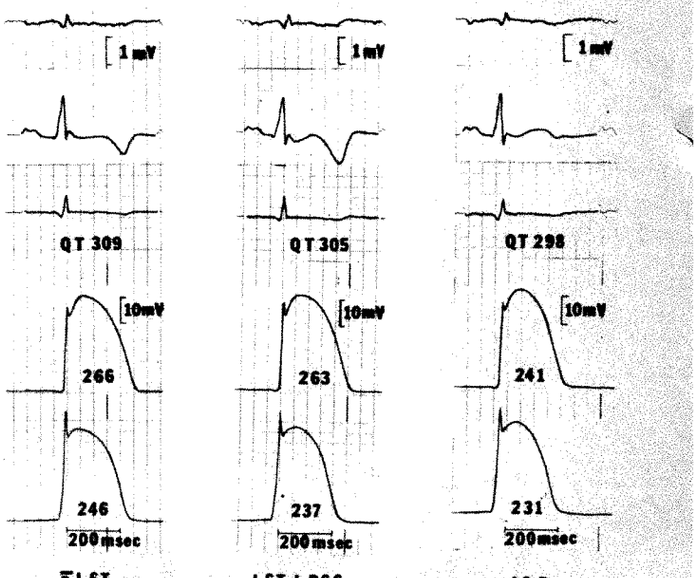

FIGURE 5. From top to bottom, leads X, Y, and Z and monophasic action potential on the posterior and anterior walls of the left ventricle. Effects of left stellate ganglion transection (LST) alone (**left panel**), subsequent right stellate ganglion stimulation (RSS) (**middle panel**) and administration of isoproterenol (ISP) (3 μg) after right stellate ganglion stimulation (**right panel**). See text. Tracings retouched for clarity.

and accelerated the recovery from the effect of right stellate ganglion stimulation. This effect of isoproterenol on the right stellate ganglion stimulation-induced Δ(A-P) was due to greater monophasic action potential shortening on the posterior than on the anterior wall.

Figure 4D correlates the changes in T wave polarity with the net effect of isoproterenol on Δ(A-P), that is, the differences between the change in Δ(A-P) without and with isoproterenol. At 30 and 60 seconds after the onset of infusion, the net effects of isoproterenol on Δ(A-P) were 8 and 12 msec, respectively; these effects were associated with reversal of T wave polarity from negative to positive. In this experiment isoproterenol accelerated the reversal of right stellate ganglion stimulation-induced changes in T wave polarity by 60 seconds. The results in other experiments were similar. The reversal of right stellate ganglion stimulation-induced T wave changes by isoproterenol was associated with a change in Δ(A-P) of +11 ± 7 msec (P <0.001).

Combined Left Stellate Ganglion Transection and Right Stellate Ganglion Stimulation

The combined effects of left stellate ganglion transection and right stellate ganglion stimulation were studied in one dog (Fig. 5). The effect of left stellate ganglion transection alone was similar to the effect shown in Figure 2. After right stellate ganglion stimulation, the T wave became more deeply inverted in the Y lead, and the Q-T interval shortened by 4 msec. The duration of the P-R interval was 110 msec before and 120 msec after left stellate ganglion transection, and 105 msec after left stellate ganglion transection plus right stellate ganglion stimulation. Administration of isoproterenol after left stellate ganglion transection plus right stellate ganglion stimulation reversed the T wave polarity and shortened the Q-T interval. This change was associated with greater monophasic action potential shortening on the posterior than on the anterior wall.

Discussion

Effects of left stellate ganglion transection and right stellate ganglion stimulation: Electrocardiographic changes induced by left stellate ganglion transection and right stellate ganglion stimulation resembled previously reported changes produced by the same or similar procedures.[5,6] In agreement with the results of Yanowitz et al.,[5] we found that left stellate ganglion transection prolonged the P-R interval, and that both left stellate ganglion transection and right stellate ganglion stimulation induced T wave inversion in the longitudinal (Y) lead without QRS changes. A similar T wave inversion in the longitudinal lead was also found by Kralios et al.[6] after stimulation of the right recurrent cardiac nerve. In our study, the T wave inversion was associated with shortening of the Q-T interval after right stellate ganglion stimulation, and with lengthening of the Q-T interval after left stellate ganglion transection. These results differ from the results of Yanowitz et al.,[5] who found "no measurable change in the Q-T interval after left stellate ganglionectomy or right stellate stimulation."

This difference in results may be due to one or more of the following factors: (1) Difference in the method of Q-T interval determination: We measured this interval in three simultaneously recorded leads, and Yanowitz et al. in only one lead. Determination from a single lead may be less accurate if the terminal T wave portion in this lead happens to be isoelectric. (2) Difference in the technique of nerve stimulation: We stimulated the intact ganglion in all experiments, and Yanowitz et al. stimulated in some experiments the intact ganglion, and in some experiments the distal ends of the cut ansa subclavia. Stimulation of the intact ganglion is more likely to be associated with a reflexly mediated stimulatory effect on the contralateral side than stimulation of the distal end of the cut nerve.[13,14] (3) Absolute magnitude of change in the duration of recovery: In many of our experiments changes in the monophasic action potential duration were greater than changes in the duration of functional refractory periods reported by Yanowitz et al. after similar procedures.

Monophasic action potentials and refractory periods: In our study, left stellate ganglion transection prolonged the monophasic action potential on the posterior wall and right stellate ganglion stimulation shortened this potential predominantly on the anterior wall of the ventricles. These changes in duration correlated well with previously reported changes in refractory periods after similar procedures, namely, lengthening on the posterior ventricular surface after left stellate ganglionectomy,[5] and shortening on the anterior wall after stimulation of the right recurrent cardiac nerve.[6]

We[9] have previously stated that consistent agreement between the changes in monophasic action potentials and the refractory periods may be expected when all ventricular action potentials (1) exhibit the same relation between the recovery of excitability and the membrane potential, (2) have the same slope of phase 3, and (3) differ from each other in duration only because of different durations of phase 2. Our previous studies showed that all monophasic action potentials on the ventricular surface had the same slope of phase 3[9] and that monophasic action potential shortening caused by isoproterenol was due almost exclusively to the shortening of phase 2.[10] In addition, our present study shows that right stellate ganglion stimulation shortened the monophasic action potential without changing the slope of phase 3. This observation may explain the agreement between the changes in duration of the monophasic action potential and the durations of refractory periods after stimulation of right-sided cardiac nerves.[6] Our study provides additional evidence that the refractory periods faithfully represent the sequence of ventricular repolarization.

Changes in monophasic action potential duration and Q-T interval: In this study, all procedures changed the durations of the monophasic action potential and the Q-T interval in the same direction. These durations shortened after administration of isoproterenol (Tables I and III) or right stellate ganglion stimulation (Table IV) and lengthened after left stellate ganglion tran-

section (Table II). As expected, the agreement between the absolute change in duration of the Q-T interval and the change in duration of the monophasic action potential was closer after procedures that induced regional lengthening of the potential (Table II) or global shortening of it (Tables I and III) than after procedures that induced predominantly regional shortening of the monophasic action potential (Table IV). These results are consistent with those of previous experiments that showed no evidence of "silent" repolarization after the end of the T wave.[9,10]

Changes in monophasic action potential duration and T wave polarity: Uniform shortening of the monophasic action potential in control experiments was associated with shortening of the Q-T interval but no consistent change in T wave polarity. The reversals of T wave polarity induced by left stellate ganglion transection, right stellate ganglion stimulation and administration of isoproterenol after left stellate ganglion transection were associated with an average change in Δ(A-P) of 13 to 17 msec. The average change in the Q-T interval after these three procedures ranged from 14 to 19 msec. The similar magnitude of the changes in Δ(A-P) and the Q-T interval suggests that the monophasic action potential in the intramural or subendocardial regions did not lengthen more or shorten less than the monophasic action potential on the ventricular surface. In some experiments, reported previously,[10] we found no difference between the magnitude of isoproterenol-induced shortening of the monophasic action potential in different layers of the ventricular wall. Our findings provide additional evidence that the T wave is a sensitive indicator of relatively small changes in duration of the action potential.[15]

"Normalization" of neurogenic T wave abnormalities: clinical implications: Isoproterenol changed T wave polarity and restored the control T wave configurations after both left stellate ganglion transection and right stellate ganglion stimulation. In each case, isoproterenol produced unequal shortening of the monophasic action potential on the anterior and posterior walls of the ventricle and thereby restored the normal relation between their durations. After left stellate ganglion transection, isoproterenol shortened the previously prolonged monophasic action potential more than the control potential; after right stellate ganglion stimulation, it shortened the control potential more than the previously shortened potential.

If the results of our experiments in dogs are applicable to man, normalization of the T wave after administration of isoproterenol may be expected in all cases of primary T wave changes (1) induced by regional shortening of ventricular action potentials, or (2) induced by regional lengthening of ventricular action potentials, provided that the latter are susceptible to the shortening effect of the drug. We assume that one or both of these two mechanisms account for the high incidence rate of isoproterenol-induced T wave normalization in persons with T wave abnormalities of diverse origins and different Q-T intervals.[7] On the other hand, the lack of T wave normalization in patients after myocardial infarction or pericarditis[7] may be attributed to an inadequate shortening effect of isoproterenol on the abnormally prolonged action potentials.[16]

Pathogenesis of the neurogenic T wave abnormalities in man: The typical electrocardiographic pattern of cerebrovascular accident characterized by a conspicuous increase in T wave amplitude, prolongation of the Q-T interval by 20 percent or more, and an occasional increase in U wave amplitude is not common among patients with central nervous system diseases. We found this pattern in 32 percent of patients with intracranial hemorrhage and in less than 10 percent of patients with other central nervous system diseases.[15] However, an identical pattern may appear after transabdominal truncal vagotomy for treatment of peptic ulcer disease[17] or after assumed destruction of the sympathetic nerve fibers during radical lymph node dissection of the right side of the neck.[18]

Unilateral stimulation of right-sided cardiac nerves would not be expected to produce a typical pattern of cerebrovascular accident since in our study this procedure shortened the Q-T interval. Left stellate ganglion transection prolonged the Q-T interval, but it also prolonged the P-R interval, which is usually shortened in the typical human pattern of cerebrovascular accident.[19] The pattern most similar to that of cerebrovascular accident in man appeared in the experiment with combined left stellate ganglion transection and right stellate stimulation (Fig. 5). This procedure induced a conspicuous change in T wave amplitude, prolongation of the Q-T interval and shortening of the P-R interval. This similarity suggests that the pattern of cerebrovascular accident in man may be due to some combination of stimulation and inhibition of different portions of sympathetic centers, presumably in the hypothalamus. Further studies will be needed to test this assumption and to elucidate the precise mechanism or mechanisms of the typical pattern of cerebrovascular accident in man.

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Cardiac Dysrhythmias in the Conscious Dog After Surgically Induced Autonomic Imbalance

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The ventrolateral cardiac nerve in the dog is a primary branch of the left sympathetics and represents a direct neural link between the central nervous system and the heart. Its electric excitation elicits characteristic shifts in pacemaker and tachydysrhythmias related to its explicit innervation of the inferior atrial, atrioventricular (A-V) junctional and ventricular tissues. Total denervation of the canine heart, sparing the ventrolateral cardiac nerve, produced a long-term model in which only these portions of the heart retained their sympathetic innervation. The trained unanesthetized model dog was subjected to severe exercise in order to determine the effects of elevated levels of sympathetic tone upon these important regions of the conduction system. Reproducible tachydysrhythmias were elicited in all six animals completing the regimen of periodic testingover a period of 136 to 378 days after operation. The abnormal rhythms consisted of shifting cardiac pacemakers and supraventricular A-V junctional and ventricular tachycardias with frequent premature systoles. Comparable abnormalities were not observed in a similarly tested sham-operated animal or in dogs with a totally denervated heart. The exercise-induced dysrhythmias gradually disappeared with time, presumably in relation to autonomic reinnervation of the heart. The characteristic patterns of dysrhythmia are explainable on the basis of anatomic distribution of the ventrolateral cardiac nerve and upon its presumed influence upon Purkinje fiber and A-V nodal automaticity and temporal dispersion of refractoriness in myocardial tissues.

Recent reports from this laboratory[1–6] have described the distribution of the autonomic cardiac nerves in the dog and presented evidence that the majority of nerves enter the heart along the superior vena cava, around the great arteries, and project onto the superior surfaces of the right and left atria. Fibers of left-sided origin also enter the heart laterally from the ventrolateral cardiac nerve. Differential distribution to the sinoatrial (S-A) and atrioventricular (A-V) nodes[2] suggests that one might selectively deprive one or the other of these important cardiac regions of its innervation, thus disrupting the balance of autonomic supply.

Neurally induced sinus tachycardia requires intact innervation of the S-A node. Dysrhythmias of nodal (or junctional) origin may be elicited by direct electric excitation of selected thoracic nerves after ablation of the S-A nodal and atrial nerve supply. It is thus possible to drive the A-V node and junctional pacemakers to high rates by stimulating the ventrolateral cervical cardiac nerve or infusing norepinephrine.[2,7–9] Furthermore, it has been shown that adrenergic activation is capable of increasing automaticity in Purkinje fibers, increasing temporal dispersion of refractoriness in ventricular muscle[10] and greatly increasing refractoriness of terminal Purkinje fibers.[11] It is therefore conceivable that "imbalance" in nerve supply to these regions may play an important role in the onset and maintenance of junctional or ventricular dysrhythmias.

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This paper describes the preparation of a canine model in which the S-A node and atrial tissues are totally denervated while the A-V nodal region and the left ventricular myocardium retain a portion of their sympathetic nerve supply. Responses of such a model dog to direct electric stimulation of the intact ventrolateral cardiac nerve as well as responses of the nonanesthetized animal severely stressed during treadmill exercise reveal the electrophysiologic results of such "imbalanced" cardiac innervation.

Methods

Mongrel dogs of either sex weighing approximately 20 kg were lightly anesthetized with intravenously administered sodium pentobarbital (30 mg/kg) and placed on positive pressure respiration. With aseptic procedures, the heart was exposed through a left thoractomy, both thoracic vagi were isolated immediately distal to the caudal cervical ganglion, and the right and left stellate ganglia were prepared for electric stimulation. Walton-Brodie strain gauge arches were sutured to the right atrial and right ventricular conal surfaces, and small bipolar silver electrodes were applied epicardially over the S-A node, the inferior right atrium and the right ventricular conus. A lead II electrocardiogram and systemic arterial blood pressure were also recorded on an eight channel model 7 Grass polygraph. Square wave stimulation pulses were delivered to the thoracic vagi (20 hertz, 5 msec, 4 to 6 volts) and to the stellate ganglia (10 hertz, 5 msec, 4 to 6 volts) from a Grass model S5 stimulator. Stimulation variables were monitored on a Hewlett-Packard 120 B oscilloscope. Recordings were made, with and without autonomic nerve stimulation, before and immediately after surgical ablation of the S-A nodal, atrial and a portion of ventricular autonomic innervation. Whenever evidence of inotropic, chronotropic or dromotropic responses within atrial tissues remained, the sites of denervation were reexplored and surgery extended until denervation of all tissues except the A-V node and ventricular tissues was accomplished.

The surgical procedures employed included careful transection around the complete circumference of the superior vena cava, with ligation and division of the azygous vein. The dissection was continued medially from the superior vena cava across the superior surfaces of the right and left atria, and the adventitia was removed from the complete circumference of the pulmonary artery. All nervous tissue was also removed between the roots of the pulmonary artery and the ascending aorta.[12]

In some animals the bipolar electrodes were left in place upon the S-A node, inferior right atrium and right ventricle, the electrodes being brought through the chest wall and through the skin on the back of the neck. The pericardium was loosely closed, the ribs were approximated and the incision was closed in layers. Thoracentesis was used to evacuate residual air from the chest cavity. No extraordinary postoperative care was necessary except for administration of antibiotic agents. All animals were ambulatory on the 1st postoperative day and were started on treadmill exercise within 2 or 3 days.

Results

Preoperative control tracings: Figure 1 illustrates the results of electric stimulation in the open chest animal immediately before neural ablation. A normal electrocardiogram and sequence of electrical activation (the S-A electrogram first, followed by the inferior right atrial and then the right ventricular electrograms) were accompanied by appropriate contractile force recordings from the atrium and ventricle. Blood pressure was stabilized at 145/120 mm Hg and heart rate at 155 beats/min. Electric excitation of the left and right cervical vagosympathetic trunks elicited either marked bradycardia or asystole, together with depression in myocardial contractile force. Recording of an escape beat during stimulation of the right cervical vagus (middle panel) reveals retrograde spread of excitation from an abnormal focus, probably below the A-V node, with almost instantaneous development of a beat after cessation of stimulation. The latter beat was clearly supraventricular in origin, closer to the electrode on the inferior right atrium than to the S-A node, but with relatively normal transmission through the A-V node and to the ventricles. Responses to right and left stellate stimulation revealed expected alterations in heart rate and contractile force, the former with a clear supraventricular and

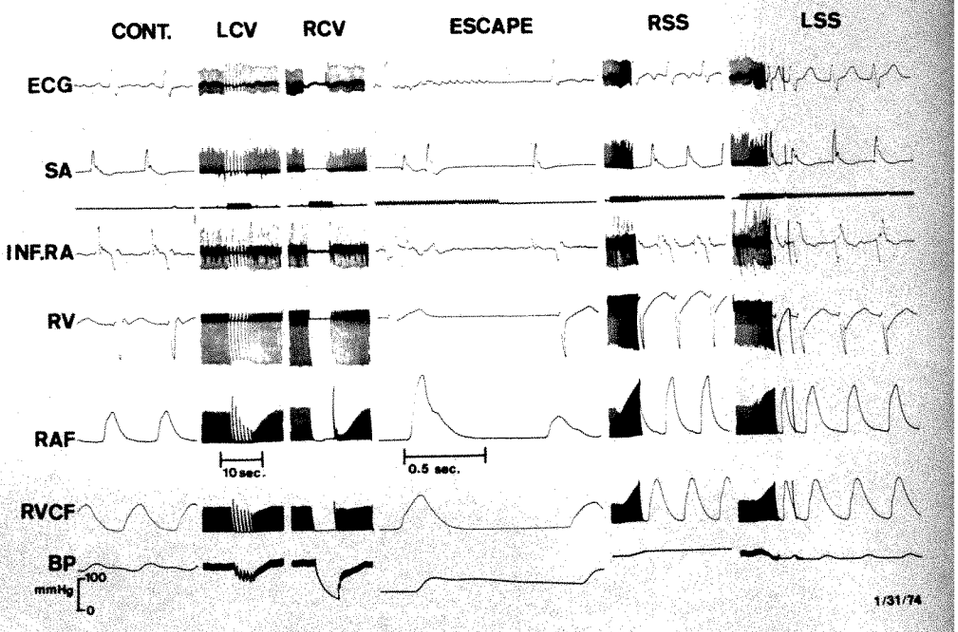

FIGURE 1. Preoperative data. Simultaneous recordings of the lead II electrocardiogram (ECG) and S-A nodal (SA), inferior right atrial (INF. RA) and right ventricular (RV) electrograms, together with contractile force from the right atrium (RAF) and right ventricular conus (RVCF) and blood pressure (BP) immediately before total denervation of the heart except for the ventrolateral cardiac nerve. Control (CONT.) records are shown at the extreme left, followed by responses to electrical stimulation (20 hertz, 5 msec, 5 v) of the right (RCV) and left (LCV) cervical vagi. An escape beat is shown followed by responses to electric stimulation (10 hertz, 5 msec, 5 v) of the right (RSS) and left (LSS) stellate ganglions.

the latter with junctional or A-V nodal origins. Thus, the preoperative responses to autonomic nerve stimulation established the existence of intact neural regulatory mechanisms and demonstrated the feasibility of acquiring definitive information concerning the origin and spread of excitation.

Postoperative tracings: Immediately after these functional recordings, the sympathetic and parasympathetic supplies to the heart, with the exception of the ventrolateral cervical cardiac nerve, were surgically transected. The identical stimulation procedures described for Figure 1 were repeated. It is not uncommon to find residual responses to nerve stimulation after the initial surgical procedures but in each animal of this study, closure was not made until all responses had been eliminated. Figure 2 illustrates the complete elimination of all effector responses to stimulation of the left and right vagi and to excitation of the right stellate ganglion. Upon left stellate stimulation, however, the immediate alteration in cardiac function indicated acceleration in heart rate with abnormal pacemaker location as in Figure 1, again probably in or near the A-V node. Direct electric excitation of the ventrolateral cardiac nerve induced a similar tachycardia, with repeated bouts of irregular electric and mechanical activity (next to last panel, Fig. 2). S-A nodal and inferior right atrial electrograms revealed multiple discharges, only some of which were conducted across the A-V node. It is thus apparent that the ventrolateral cardiac portion of the left sympathetic supply to the heart, and particularly to the A-V node, remained intact. Injection of Xylocaine® (0.5 ml, 2 percent solution) directly into the ventrolateral cardiac nerve distal to the point of stimulation eliminated this response.

Treadmill tracings: Figure 3 illustrates a type of dysrhythmia that developed in an animal standing quietly on the treadmill 1 day after surgical transection of all nerve projections onto the heart with the exception of the ventrolateral cardiac nerve. Direct electrograms revealed precedence within or close to the S-A node followed by the inferior right atrium,

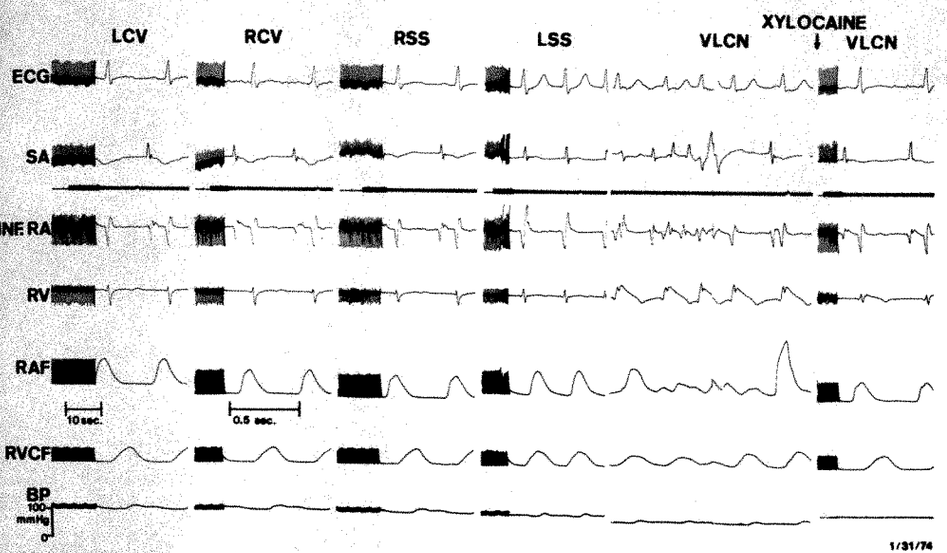

FIGURE 2. Postoperative data. Recordings as in Figure 1 after complete denervation of the heart except for the ventrolateral cardiac nerve (VLCN). Note the absence of response to stimulation of the left and right cervical vagi and right stellate ganglion. The response to left stellate ganglion stimulation is similar because of the presence of intact ventrolateral cardiac neural distribution to the heart. Characteristic dysrhythmias were also elicited by electrical stimulation of the intrapericardial ventrolateral nerve after operation, and these were eliminated by the injection of Xylocaine directly into the nerve at a point distal to the stimulating electrodes. Abbreviations as in Figure 1.

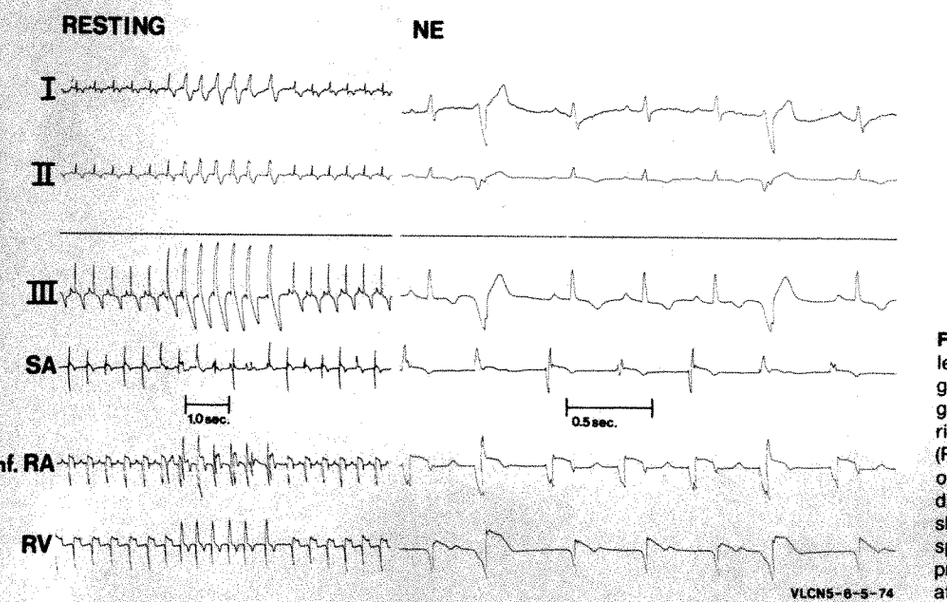

FIGURE 3. Simultaneous recordings of leads I, II and III of the electrocardiogram, together with bipolar electrograms from the S-A node (SA), inferior right atrium (Inf. RA) and right ventricle (RV) in an awake dog standing quietly on the treadmill 1 day after partial cardiac denervation. The dysrhythmia shown in the left panel developed spontaneously while the ventricular premature beats occurred repetitively after norepinephrine (NE).

both discharging at the initial upsweep of the P wave. A progressively shortening P-R interval was accompanied by simultaneous caudal movement of the supraventricular pacemaker as indicated by the atrial electrograms. Discharge from a second pacemaker situated in a junctional or ventricular site also occurred. The S-A node continued to discharge at a regular, but slightly slower, rate to emerge again as the dominant pacemaker toward the end of the panel. The right panel signals a repetitively firing ventricular pacemaker during the influence of intravenously injected norepinephrine. During the regularly recurring supraventricular beats, the pacemaker appeared to be located approximately equidistant from the S-A node and the inferior right atrial electrode, resulting in simultaneous excitation of the two atrial electrograms. Spread throughout the atria was rapid and symmetric, producing an upright P wave with a normal P-R interval and a normal QRS deflection. After three successive beats, a premature ventricular systole occurred, followed again by essentially normal supraventricular cycles.

Figure 4 illustrates the response in a dog that had sustained similar partial denervation some 50 days postoperatively. During quiet standing on the treadmill (upper panel, control), the cardiac rhythm spontaneously oscillated from a supraventricular and probably sinus rhythm to a paroxysmal tachycardia having an A-V nodal or junctional focus. The tachycardia became exaggerated during the stress of exercise. The final panel (top) demonstrates the inability of atropine to control the dysrhythmia. On the following day, the same animal (lower panels) was again subjected to treadmill exercise with resulting induction of tachycardia having a junctional focus. During the tachycardia, propranolol was injected intravenously with consequent attenuation and abolition of the dysrhythmia.

Stress-related cardiac dysrhythmias: Twelve animals were prepared by cardiac denervation sparing the ventrolateral nerve. Six of these 12 were introduced into a regular treadmill exercise regimen, and all 6 successfully completed an extended series of experiments involving exercise and treatment with pharmacologic blocking agents and procedures designed to identify the presence and mechanism of stress-related cardiac dysrhythmia. The responses of these six animals are described in Table I, together with those in a "sham operated" animal in which the chest was opened and bipolar electrodes were secured to the surface of the heart in identical fashion, but surgical denervation procedures were not carried out. Finally, four animals are included in which identical procedures were followed, except that the heart was totally denervated at the time of operation. That is, the ventrolateral cardiac nerve was transected as well as the other sympathetic and parasympathetic projections onto the heart as described in the Methods section. Cardiac dysrhythmias were induced by severe exercise, sometimes accompanied by struggling, in all six dogs with cardiac denervation but intact ventrolateral nerve but in none of the sham operated or totally denervated animals. However, dysrhythmias were not observed in every animal during every run on the treadmill, presumably because the severity of sympathetic stress developing during the exercise did not always reach sufficient intensity to disrupt normal electrical activation. The dysrhythmias consisted of pacemaker shifts, coupled beats, A-V block, premature atrial and ventricular systoles, junctional rhythms and atrial and ventricular tachycardias. In only two animals (VLCN 2 and 5) did atropine elicit acceleration in heart rate or give evidence of intact parasympathetic innervation before 45 to 60 days postoperatively. After this period, atropine regularly signaled reinnervation by way of the vagus. A-V block consistently occurred in one dog (VLCN 9) during exercise runs within the first 45 days postoperatively. Atropine regularly relieved the A-V block, and propranolol abolished the junctional dysrhythmias that developed during exercise in this animal. It is assumed that in this animal fibers from the left thoracic vagus were left intact as they swept across the pulmonary artery and into the atrial and A-V nodal regions at the level of the left superior pulmonary vein. The exercise-associated dysrhythmias became more difficult to induce 2 to 5 months after operation, presumably because of the successive reinnervation of different portions of the heart as sympathetic nerves reestablished autonomic "balance" in cardiac control. Severe exercise then resulted simply in marked tachycardia of supraventricular origin as in control and sham operated

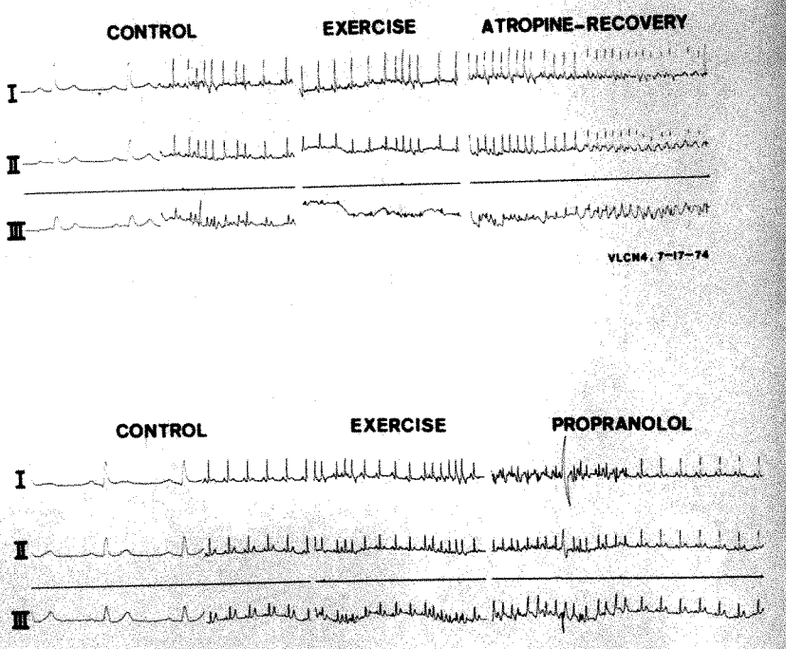

FIGURE 4. Responses in an animal with denervation except for the ventrolateral cardiac nerve 50 days postoperatively **(upper records)** during the control state and exercise, and after intravenous administration of atropine (1 mg/kg). The **bottom record** was obtained in the same animal on the following day and reveals a similar dysrhythmia exaggerated by exercise and abolished by intravenous administration of propranolol (1 mg/kg).

TABLE I

Cardiac Dysrhythmias in Long-Term Canine Model

Dog no.	Survival (days)	Type of Dysrhythmia	Comments
VLCN 1	329	Coupled ventricular PVCs; ventricular tachycardia	Evidence of a few intact parasympathetic fibers (blocked by atropine). Sinus arrhythmia present on day 304 (blocked by atropine)
VLCN 4	280	Coupled beats; shifting supraventricular pacemakers; junctional rhythm; PVCs; ventricular tachycardia	Coupled beats and shifting pacemakers present during control periods and exaggerated during exercise. Atropine without effect; propranolol caused reversion to sinus rhythm
VLCN 5	378	Shifting pacemaker; atrial fibrillation; ventricular tachycardia; junctional rhythm; coupled beats; sinus bradycardia on day 172	Multiple dysrhythmias observed during exercise. Pacemaker repeatedly shifted from supraventricular to junctional. Propranolol abolished dysrhythmia. Atropine abolished bradycardia on day 172
VLCN 6	370	Ventricular tachycardia; PVCs	Atropine had no influence until day 157, when it accelerated heart rate. Propranolol caused reversion of tachycardia to sinus rhythm
VLCN 9	162	Junctional rhythm; A-V block	A-V block consistently induced during exercise (abolished by atropine). Evidence for residual parasympathetic fibers. Propranolol abolished junctional rhythm
VLCN 10	136	PVCs; shifting pacemaker; bigeminy	P wave configuration changed, with shortening P-R interval on days 1, 2 and 4. Exercise accentuated pacemaker shifts. Atropine without effect; propranolol caused reversion to sinus rhythm
Sham 1	>1 yr	None	Pericardium opened and bipolar electrodes sutured in place. Surgical denervation not performed
Four dogs with total cardiac denervation	>1 yr	No systematic dysrhythmias	Run on treadmill in manner identical to series with intact ventrolateral cardiac nerve. No sinus arrhythmia, no response to atropine or propranolol. Slowly accelerating heart rate during exercise.

PVCs = premature ventricular contractions.

animals. All of the animals were killed at the end of the time indicated in Table I with an acute experiment in which chronotropic, inotropic and dromotropic responses to sympathetic and vagal trunk stimulation were examined. All showed significant degrees of reinnervation, ranging from nearly maximal responses in the longer recovery periods to moderate reinnervation after the shorter periods.

Discussion

The A-V node receives a generous innervation, presumably from both sympathetic and parasympathetic systems, and arrhythmias of nodal (or junctional) origin commonly result from excitation of the left stellate ganglion or selected cardiac nerves.[2,3,8] It is possible to drive the neurally isolated A-V node at excessively high rates by means of adrenergic stimulation, and the "antagonistic" actions of vagal input to this region have been demonstrated by many workers. An "imbalance" of input from these two systems could, at least in theory, play an important role in the onset and maintenance of junctional dysrhythmias. A long-term model for study of cardiac dysrhythmias related to such "imbalance" in neural control is described. This model also illustrates the existence of a neural bridge between the central nervous system and the heart and demonstrates its participation in adrenergically induced dysrhythmia.

Abildskov[13] has discussed the role of the autonomic nervous system in clinical arrhythmias and illustrated the frustrations encountered in definitely explaining cause and effect relations. Relatively few observations of ventricular dysrhythmias due to cardiac nerve stimulation have been reported. However such rhythm disturbances are much more common during activation of highly localized sites within central nervous system structures.[14–16] Centrally generated dysrhythmias may involve much more discrete autonomic activation of local areas within the myocardium than electrical stimulation of selected cardiac nerves can produce.

Mechanism of induced dysrhythmias: We cannot rule out either reentry or rapidly firing ectopic foci as the cause of the tachydysrhythmias encountered in this model. Cardiac nerves are known to be concentrated in the junctional zone[17–19] and in ventricular muscle. It is our unproved thesis that the tachydysrhythmias induced in our model are related to this distribution of fibers within the ventrolateral cardiac nerve, and that focal or even multifocal zones of hyperautomaticity and altered refractoriness may be established as a result of their excessive (or imbalanced) stimulation.

The recent observation by Urthaler and James[20] that Tetrodotoxin® produces vagal and sympathetic neural blockade in the A-V junction, but does not block the direct actions of acetylcholine or norepinephrine suggests this substance in proper dose levels may provide important insights into the mechanisms of dysrhythmias induced by the ventrolateral cardiac nerve. Urthaler and his group[21] have also demonstrated that both escape time and rate of escape rhythm are impaired by interruption of adrenergic neural influence upon either the sinus node or A-V junction. Selective beta blockade slowed the sinus rhythm by 10 percent, but slowed the A-V junctional rhythm by 43 percent. Thus, it is clear that both of these automatic centers in

the heart are markedly influenced by adrenergic neural tone, but the A-V junction appears to be more dependent than the sinus node.

Spear and Moore[22] have observed that an important factor involved in "wandering pacemakers" and the emergence of single or multiple ectopic beats during increased autonomic activity is the differing sensitivity levels and response characteristics of the various potential pacemaker sites. They state that because A-V nodal conduction is sensitive to changes in rate and rhythm, autonomic influences can indirectly affect the character of A-V conduction by the changing coupling intervals. Even during constant pacing, changes in A-V conduction time modified the effective coupling interval at which subsequent beats were conducted. Our experiments suggest a further complication of these phenomena in the event of damage to either the vagal or sympathetic component and resulting "imbalance" in neural influence upon selected portions of the conducting system.

Implications of study: The specific distribution of the ventrolateral cardiac nerve to A-V junctional and ventricular regions of the canine heart[2] is of key importance in the development of the model described. Electrical stimulation of this nerve displaces the pacemaker from high right atrial sites to inferior atrial or junctional regions in approximately 70 percent of dogs tested.[23,24] Its stimulation is also characterized by facilitation of conduction through the A-V node, and Spear and Moore[22] have called attention to the subliminal effects on A-V conduction that may be brought out during conduction of premature atrial beats. Furthermore, activation of the ventrolateral cardiac nerve through left stellate ganglion stimulation should be expected to increase Purkinje fiber automaticity[9] and temporal dispersion of refractoriness in ventricular muscle.[10] Thus, the animal model described should have many uses in demonstrating ways in which the autonomic nervous system may play a significant role in inducing cardiac dysrhythmia.

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Effect of Nitroglycerin on Ventricular Fibrillation Threshold of Nonischemic Myocardium

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The threshold for ventricular fibrillation induced by a 200 msec train of pulses was measured during a control period and during an intravenous infusion of nitroglycerin in 14 nonischemic open chest dogs. Infusion of nitroglycerin in doses sufficient to reduce mean arterial blood pressure an average of 17 mm Hg was associated with a rise in ventricular fibrillation threshold from a control value of 24 ± 3 (mean ±1 standard error of the mean) to 41 ± 6 milliamperes ($P < 0.001$). In a subgroup of six animals simultaneous infusions of nitroglycerin and phenylephrine abolished the hypotensive effect of nitroglycerin but did not significantly alter the rise in ventricular fibrillation threshold observed with nitroglycerin infusion alone. In five other animals mean arterial blood pressure was similarly reduced an average of 17 mm Hg by venous hemorrhage, but was associated with a lowering rather than a rise in ventricular fibrillation threshold from a prehemorrhage value of 28 ± 6 to 15 ± 2 milliamperes, ($P < 0.005$). Thus, intravenously administered nitroglycerin raises ventricular fibrillation threshold in nonischemic canine myocardium independent of its hypotensive effects.

In addition to its time-honored role as an antianginal agent, nitroglycerin has been shown to improve left ventricular function in patients with acute myocardial infarction.[1,2] Furthermore, it reduces myocardial ischemia[1,3–5] and enhances ventricular electrical stability[6–8] after ischemic injury in man and in the experimental animal.

Recently, it has been shown that nitrates can improve left ventricular function in patients without ischemic heart disease.[9] The purpose of this investigation was to determine whether nitroglycerin can also alter the electrical stability of nonischemic myocardium, as measured by the ventricular fibrillation threshold.

Methods

Twenty-two mongrel dogs weighing 22 to 36 kg were anesthetized with intravenously administered sodium pentobarbital, 30 mg/kg body weight. The animals were intubated and ventilated with a Harvard respirator using room air. The heart was exposed through a median sternotomy and suspended in a pericardial cradle. Heart rate was kept constant by crushing the sinus node and pacing from the atria with bipolar plunge electrodes at a constant cycle length of 400 msec (150 beats/min). Systemic arterial and left ventricular pressures were recorded by means of catheters placed in the central aorta and in the left ventricle utilizing Statham P23Db pressure transducers.

The fibrillating current was delivered through a bipolar platinum plaque electrode sutured with 5-0 silk to the left ventricular epicardium; the two electrodes were each 1 mm in diameter and were separated by an interelectrode distance of 5.5 mm. The current consisted of a train of 20 pulses, each 2 msec in duration and 8 msec apart, for a total duration of 200 msec. The pulse train was synchronized with the lead II surface electrocardiogram and was programmed to begin 50 msec after the onset of the last paced QRS complex every 15 paced beats. After delivery of the pulse train, pacing was interrupted for one basic cycle length and was then resumed. With use of a constant current source,

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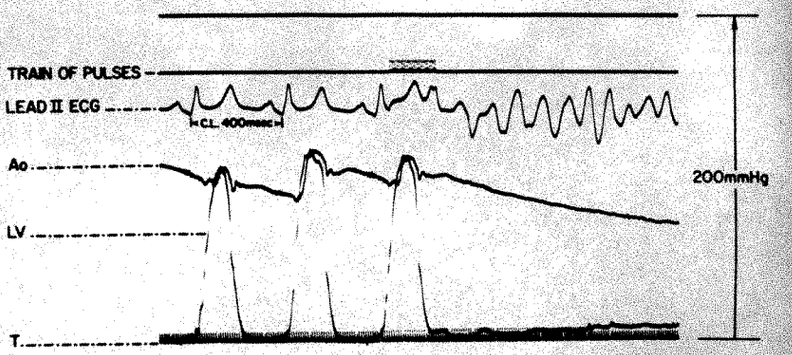

FIGURE 1. Direct recording of electrical pulse train, lead II surface electrocardiogram (ECG), central aortic (Ao) and left ventricular (LV) pressures, and 10 msec time lines (T). Full scale 200 mm Hg pressure calibration is shown to the right. The basic cycle length (CL) is 400 msec. The pulse train occurs after the third paced QRS complex and results in ventricular fibrillation.

the strength of the pulse train was increased by 1 milliampere increments until ventricular fibrillation occurred (Fig. 1). The least amount of current required to produce ventricular fibrillation, measured as the voltage drop across a known 1 kilo ohm resistor, was taken as the ventricular fibrillation threshold. The heart was then defibrillated with 10 to 20 watt seconds of direct current within 10 seconds. A 15 minute recovery period was permitted between consecutive ventricular fibrillation threshold determinations. For all treated animals ventricular fibrillation threshold values represent the average of two to four consecutive determinations.

Arterial blood gases and body temperature were monitored periodically. Arterial pH was maintained between 7.35 and 7.45 by regulating the respiratory rate and tidal volume settings of the Harvard respirator. Only one animal required intravenous administration of sodium bicarbonate (total of 35 mEq) to maintain arterial pH above 7.35. Arterial oxygen tension was kept above 60 mm Hg without the need for supplemental oxygen. Body temperature was maintained between 36° to 38° C with the use of a heating blanket.

Ventricular fibrillation threshold was measured under the following conditions:

Control: In three normotensive animals ventricular fibrillation threshold was measured at 15 minute intervals before and during the infusion of 5 percent dextrose in water, the vehicle in which nitroglycerin was dissolved. The infusion rates (0.5 to 2 ml/min) and the duration of the experiments were comparable to those used in animals treated with nitroglycerin.

Nitroglycerin: Ventricular fibrillation threshold was measured during a control period in 14 normotensive animals. Nitroglycerin (75 μg/ml of 5 percent dextrose in water) was then administered at increasing infusion rates by Harvard infusion pump until systolic arterial pressure decreased to 15 to 20 mm Hg below the control level. Thereafter, the infusion was maintained at a constant rate, and ventricular fibrillation threshold measurements were repeated 5 minutes after the desired reduction in pressure was achieved. The average final infusion rate of nitroglycerin was 46.5 μg/min (range 13.2 to 129 μg/min).

Nitroglycerin plus phenylephrine: In a subgroup of six animals the nitroglycerin infusion was continued, and ventricular fibrillation threshold was remeasured 5 minutes after systolic arterial pressure was restored to control levels by the simultaneous infusion of phenylephrine. The average final infusion rate of phenylephrine was 21.7 μg/min (range 15.3 to 38 μg/min). Final ventricular fibrillation threshold measurements were obtained 90 minutes after both drug infusions were discontinued. The total time during which ventricular fibrillation threshold was measured did not exceed 6 hours in any animal.

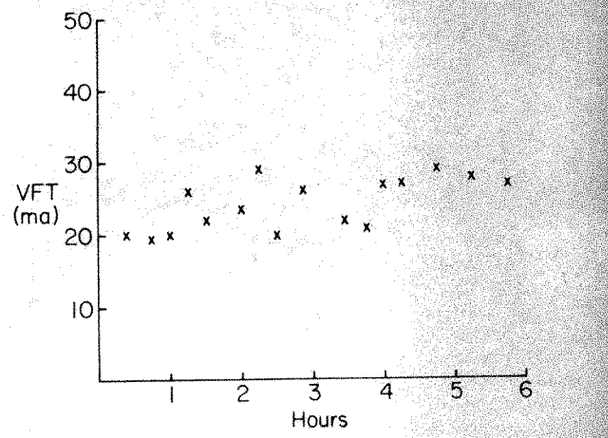

FIGURE 2. Ventricular fibrillation threshold (VFT) determinations in a control animal during a 6 hour infusion of 5 percent dextrose in water. Time in hours is shown along the abscissa. Ventricular fibrillation threshold in milliamperes (ma), shown along the ordinate, varied by less than 10 ma during the experimental period.

Venous hemorrhage: In five additional normotensive animals ventricular fibrillation threshold was determined during a control period and after venous hemorrhage. Venous hemorrhage was accomplished by withdrawal of 15 ml of blood/min from a femoral vein until systolic arterial pressure was decreased to 15 to 20 mm Hg below the control level. The degree of hypotension was comparable to that achieved in the nitroglycerin-treated animals.

Statistical analysis was performed by Student's *t* test for paired data. Results are expressed as mean values ±1 standard error of the mean.

Results

Control: In the three control animals the range of ventricular fibrillation threshold was less than 10 milliamperes before and during a 6 hour infusion of 5 percent dextrose in water (Fig. 2).

Nitroglycerin treatment: In the 14 animals treated with nitroglycerin alone, ventricular fibrillation threshold increased from an average control value of 24 ± 3 to 41 ± 6 milliamperes during infusion of nitroglycerin ($P < 0.001$), whereas mean aortic pressure decreased an average of 17 mm Hg (from 108 ± 4 to 91 ± 3 mm Hg, $P < 0.001$) (Fig. 3). The mean final infusion rate of nitroglycerin used to achieve this reduction in mean arterial pressure was 46 ± 5 μg/min.

In the six animals treated with simultaneous infusions of nitroglycerin and phenylephrine, nitroglycerin infusion alone was associated with a rise in ventricular fibrillation threshold from a control value of 26 ± 7 to 50 ± 10 milliamperes (P <0.005), whereas the mean arterial pressure decreased from 102 ± 5 to 87 ± 5 mm Hg (P <0.001, Fig. 4). When the hypotensive effect of nitroglycerin was abolished by simultaneous infusion of phenylephrine, ventricular fibrillation threshold remained significantly higher than the control level (42 ± 10 milliamperes, P <0.025). The ventricular fibrillation threshold for simultaneous drug infusions was not significantly different from the value for nitroglycerin infusion alone. Ninety minutes after both drug infusions were discontinued, ventricular fibrillation threshold returned to 27 ± 10 milliamperes, a value not significantly different from the control value, although mean arterial pressure was slightly but significantly lower than the control level (93 ± 6 mm Hg, P <0.01). Left ventricular filling pressure tended to decrease in parallel with changes in mean aortic blood pressure. Left ventricular end-diastolic pressure, measured in four animals, averaged 5 mm Hg during the control period and decreased to a mean of 2 mm Hg during infusion of nitroglycerin. During simultaneous infusion of nitroglycerin and phenylephrine, it returned to a mean of 5 mm Hg and remained at that level 90 minutes after both drug infusions were discontinued.

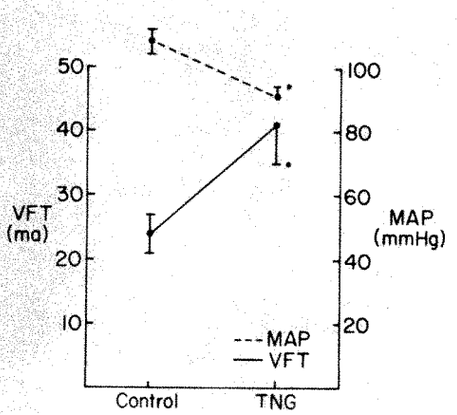

FIGURE 3. Effect of an intravenous infusion of nitroglycerin (TNG) on ventricular fibrillation threshold (VFT) and mean aortic blood pressure (MAP) in 14 normotensive animals. Measurements were obtained during a control period and during an intravenous infusion of nitroglycerin. **Left ordinate** and **solid line** depict ventricular fibrillation threshold in milliamperes (ma); **right ordinate** and **broken line** depict mean aortic blood pressure in mm Hg. Values are expressed as the mean ±1 standard error of the mean. *P <0.001 compared with control level. There is a significant increase in ventricular fibrillation threshold and reduction in mean aortic blood pressure during infusion of nitroglycerin.

Venous hemorrhage: In the animals undergoing venous hemorrhage, mean arterial pressure was reduced an average of 17 mm Hg (from 99 ± 5 to 82 ± 6 mm Hg, P <0.001), and left ventricular end-diastolic pressure, measured in four animals, decreased from a mean of 4 to a mean of 2 mm Hg. In contrast to findings in the nitroglycerin-treated group this reduction in mean arterial pressure and left ventricular end-diastolic pressure was accompanied by a lowering rather than a rise in ventricular fibrillation threshold (from 28 ± 6 milliamperes in the control period to 15 ± 2 milliamperes after venous hemorrhage, P <0.005) (Fig. 5).

Discussion

Nitroglycerin has been shown to enhance the electrical stability of acutely ischemic myocardium. In the experimental animal intravenously administered ni-

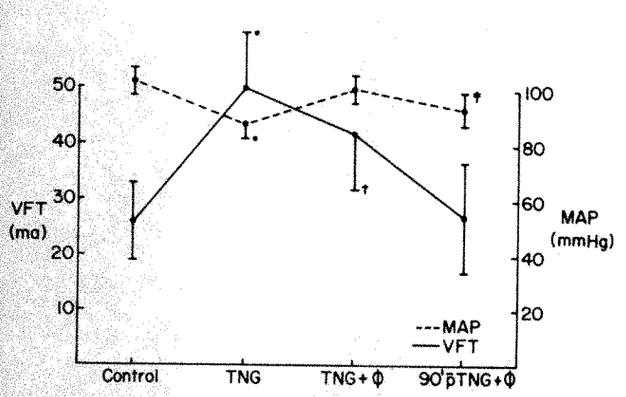

FIGURE 4. Effect of simultaneous intravenous infusions of nitroglycerin and phenylephrine on ventricular fibrillation threshold in six animals. Values were obtained during a control period, during nitroglycerin infusion alone (TNG), during simultaneous infusions of nitroglycerin and phenylephrine (TNG + ϕ), and 90 minutes after both drug infusions were discontinued (90′ p̄TNG + ϕ). Abbreviations and display as in Figure 3. *P <0.005; †P <0.025; ‡P <0.01 compared with control values. Ventricular fibrillation threshold remained significantly higher than control values during simultaneous infusion of nitroglycerin and phenylephrine despite restoration of mean aortic blood pressure to control levels. Ventricular fibrillation threshold returned to control values 90 minutes after discontinuation of both drug infusions although mean aortic blood pressure was significantly below control level at the termination of the experiments.

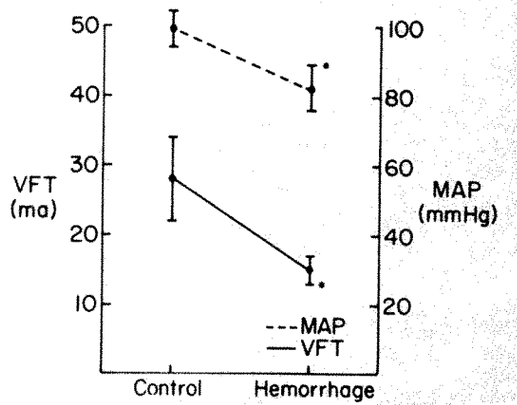

FIGURE 5. Effect of venous hemorrhage on ventricular fibrillation threshold and mean aortic blood pressure in five nonischemic normotensive animals. Values were obtained during a control period and after venous hemorrhage. Abbreviations and display as in Figure 3. *P <0.005 compared with control value. Note the significant reduction in ventricular fibrillation threshold accompanying venous hemorrhage despite hypotension similar to that produced in the nitroglycerin-treated animals.

troglycerin has been found to raise the ventricular fibrillation threshold[6] and to reduce the incidence of spontaneous ventricular fibrillation[7] after acute coronary ligation. Furthermore, sublingually administered nitroglycerin has been reported to decrease the frequency of ventricular premature beats during the first 24 hours after acute myocardial infarction in man.[8] This increase in electrical stability has been attributed to a reduction in myocardial ischemia accompanying administration of nitroglycerin.[1,3–5] However, the results of our study show that the electrophysiologic effects of nitroglycerin do not require the presence of myocardial ischemia. Intravenous administration of nitroglycerin in doses sufficient to cause a decrease of 17 mm Hg in mean arterial pressure resulted in a significant rise in ventricular fibrillation threshold above control values in a group of nonischemic normotensive animals. In three control animals given nitroglycerin in 5 percent dextrose in water at comparable infusion rates, ventricular fibrillation threshold measurements were shown to be reproducible over a similar time period of 6 hours.

Our findings also suggest that the effect of nitroglycerin on ventricular fibrillation threshold is largely independent of this drug's peripheral hemodynamic effects. During simultaneous infusion of phenylephrine, an alpha adrenergic agonist, ventricular fibrillation threshold remained significantly higher than control values, although mean arterial and left ventricular end-diastolic pressures were restored to pretreatment control levels. Kent et al.[6] noted similar findings in the ischemic canine preparation. In their study, when phenylephrine was added to nitroglycerin in a dose sufficient to restore arterial pressure to control levels, the rise in ventricular fibrillation threshold persisted or was enhanced.

In our investigation the effect of hypotension on ventricular fibrillation threshold was also studied using venous hemorrhage to reduce systemic arterial and left ventricular filling pressures to a level similar to that achieved with infusion of nitroglycerin. Hypotension induced by hemorrhage was associated with a significant lowering of ventricular fibrillation threshold compared with the rise in threshold produced by infusion of nitroglycerin. Smith et al.[10] reported analogous findings after acute coronary ligation in dogs. They noted a decrease in the sum of epicardial S-T elevations (ΣST) when afterload was reduced by nitroglycerin, but an increase in ΣST when hypotension was induced by hemorrhage. Thus, hypotension and a decrease in venous return as such appear to have adverse influences on the electrical stability of normal myocardium as well as unfavorable effects on acutely ischemic myocardium. The relation between hemorrhage and ventricular fibrillation threshold is obviously complex, since hemorrhage can result in ischemia or increased sympathetic discharge, or both, which can, in themselves, lower ventricular fibrillation threshold.[11–13] However, these variables are apparently less important during nitroglycerin-induced hypotension, since in our study ventricular fibrillation threshold increased despite a reduction in mean arterial pressure.

Mechanisms of Action

Reduced myocardial wall tension, oxygen consumption and left ventricular volume: The precise mechanism by which intravenously administered nitroglycerin raises the threshold for ventricular fibrillation is uncertain. Nitroglycerin reduces venous return to the heart by causing peripheral venous dilatation.[14] This results in a decrease in left ventricular end-diastolic pressure and volume and, by the Laplace relation, in a reduction in intramyocardial wall tension.[15] A further reduction in myocardial wall tension is achieved through a decrease in mean arterial blood pressure consequent to peripheral arterial dilatation. This reduction in wall tension results in a decrease in myocardial oxygen consumption. It is conceivable that a reduction in myocardial wall tension and oxygen consumption might improve intramyocardial conduction and diminish the dispersion of effective refractory periods, thereby enhancing the resistance to ventricular fibrillation. However, our data on simultaneous infusion of nitroglycerin and phenylephrine tend to disprove this mechanism since ventricular fibrillation threshold remained significantly higher than control values even though wall tension determinants rose to pretreatment levels. It is also possible that a decrease in left ventricular volume might alter the contact between the stimulating electrodes and the myocardium, and thus increase the required current strength to produce ventricular fibrillation. This mechanism also seems unlikely in view of our studies with venous hemorrhage, which revealed a lowering of ventricular fibrillation threshold despite a decrease in left ventricular filling pressure and, presumably, ventricular size.

Increased myocardial perfusion: Nitroglycerin may also act through a direct effect on the coronary circulation to increase oxygen supply to relatively underperfused subendocardial regions of myocardium.[16] Using radioactive microspheres, Becker et al.[17] demonstrated in dogs that after coronary ligation intravenously administered nitroglycerin causes a significant redistribution of myocardial blood flow from epicardial to endocardial layers. This increase in subendocardial perfusion occurs in both nonischemic and ischemic areas of myocardium, and it persists even after systemic blood pressure and heart rate have returned to control levels. Winbury[18] similarly showed that intravenously administered nitroglycerin can produce a selective increase in endocardial PO_2 tension in the absence of any significant increase in overall coronary blood flow. The extent to which regional changes in coronary blood flow affect ventricular fibrillation threshold is unknown, although one might anticipate more uniform conduction and less dispersion of effective refractory periods when endocardial blood flow and oxygen delivery are enhanced.

Vagal stimulation: Another possible mechanism of action of nitroglycerin may be an effect on autonomic innervation to the heart. Although reflex tachycardia often accompanies administration of nitroglycerin, bradycardia responsive to atropine has also been re-

ported,[19,20] suggesting a possible vagal stimulating effect for nitroglycerin. Stimulation of cervical vagi, independent of changes in heart rate, has been shown to increase ventricular fibrillation threshold in the nonischemic canine model[21] although the electrophysiologic basis for this effect is unclear.

Clinical Implications

Our results demonstrate that nitroglycerin raises the threshold for ventricular fibrillation in nonischemic canine myocardium. This effect appears to be independent of the peripheral hemodynamic effects of nitroglycerin and may be related to direct effects on the coronary circulation. The applicability of these experimental findings to the clinical situation is uncertain, since the relation between ventricular fibrillation threshold as a laboratory measurement and the vulnerability to spontaneous ventricular arrhythmias is complex and poorly understood.[11,22–26] Further studies appear warranted to determine whether nitroglycerin has potential usefulness in nonischemic conditions complicated by ventricular irritability.

Acknowledgment

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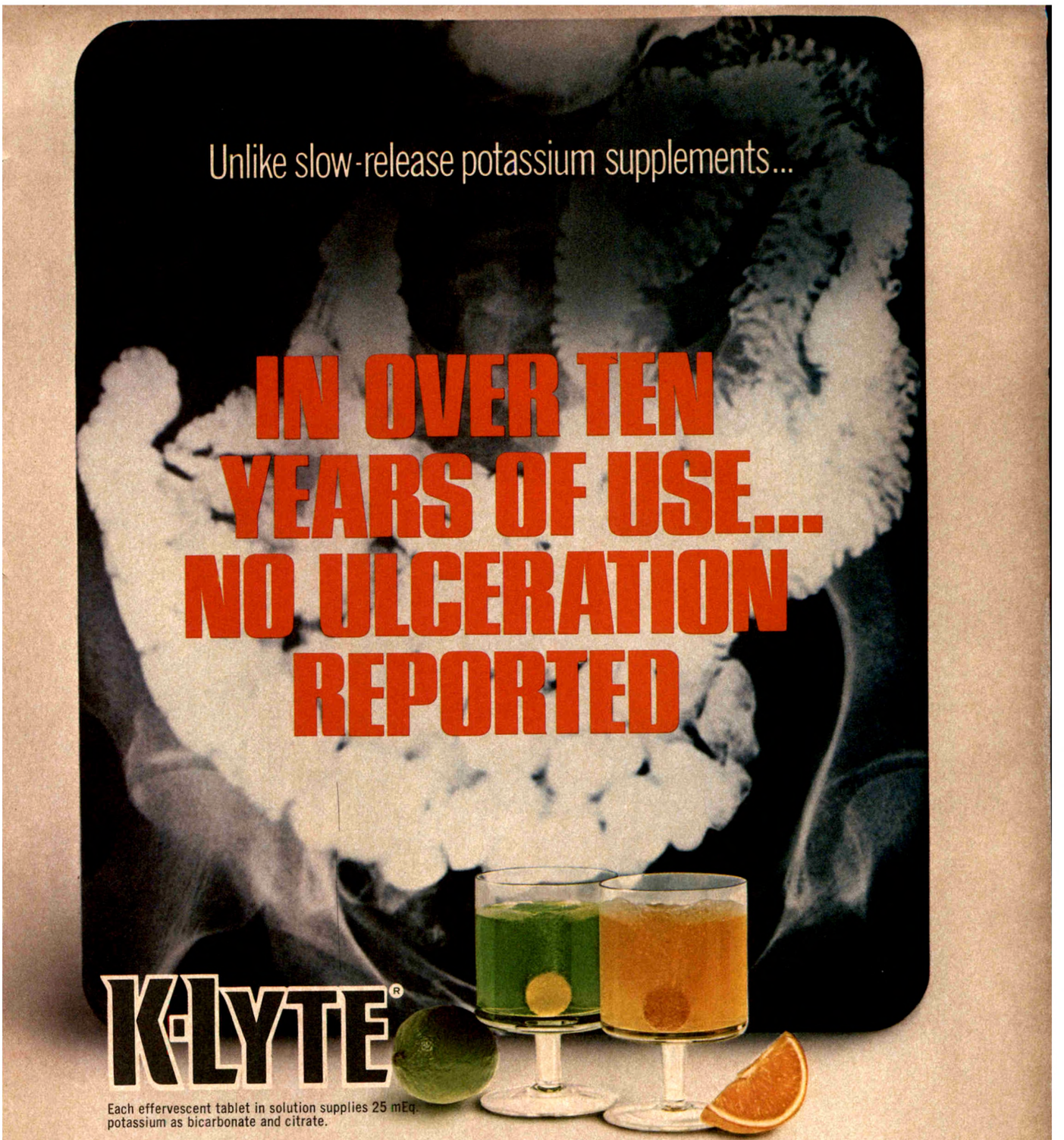

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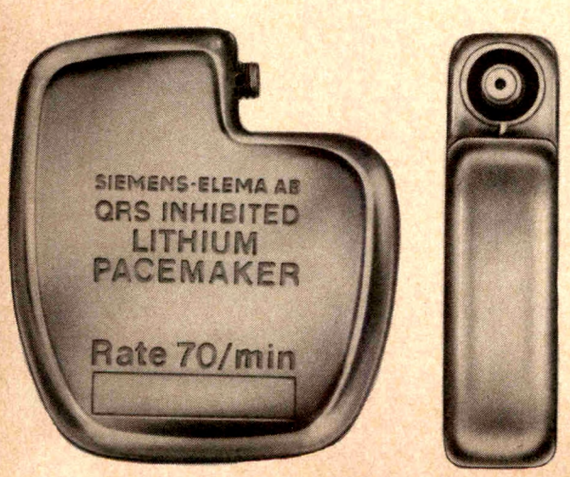

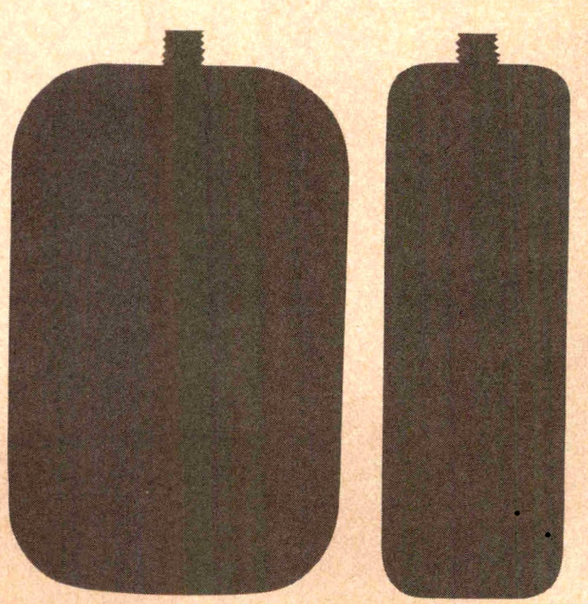

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A43

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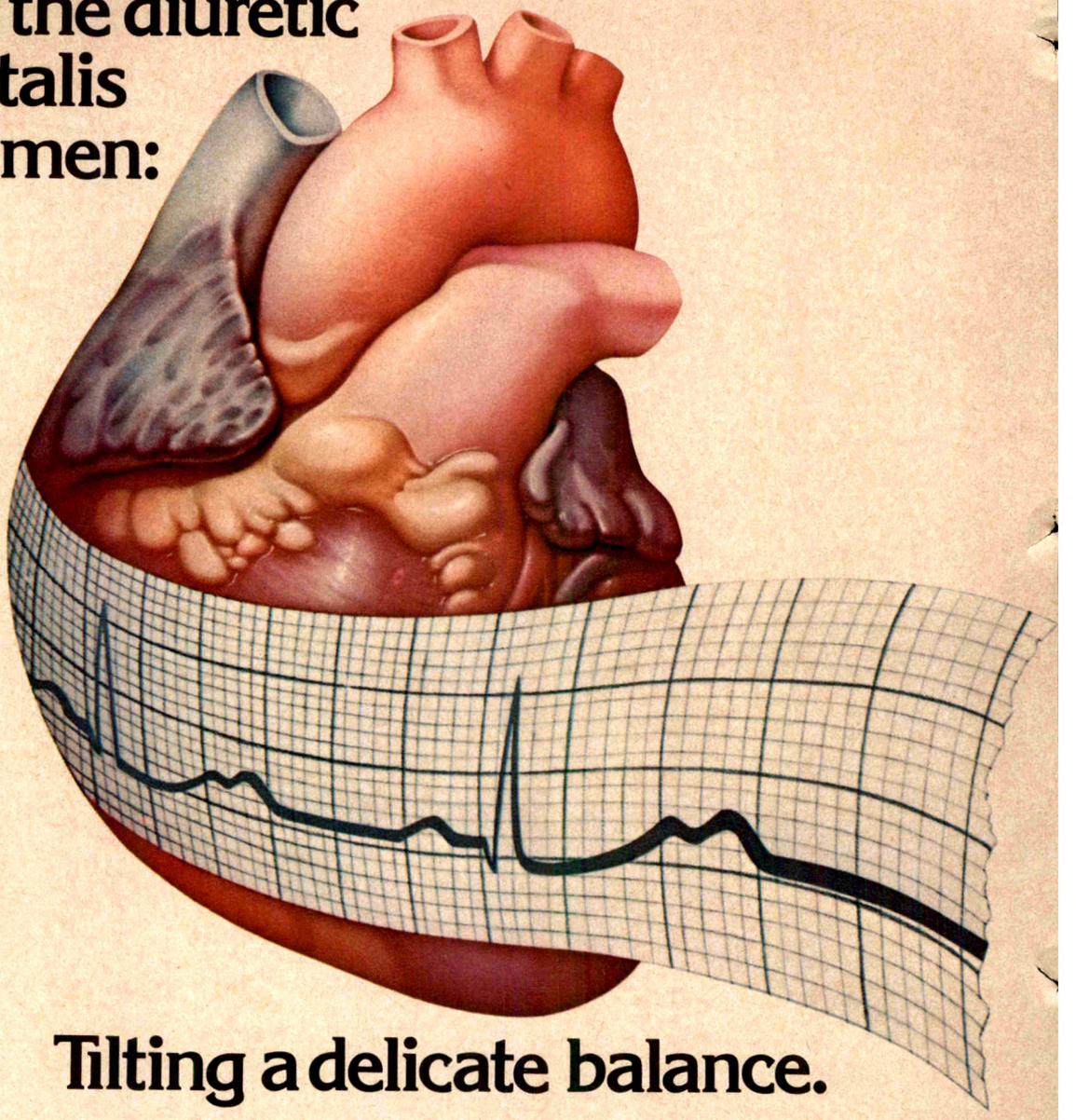

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Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).
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Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation.

Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.
Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.
Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).
Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.
Dosage and Administration: Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.

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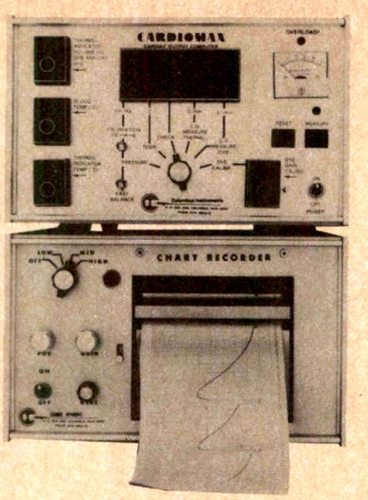

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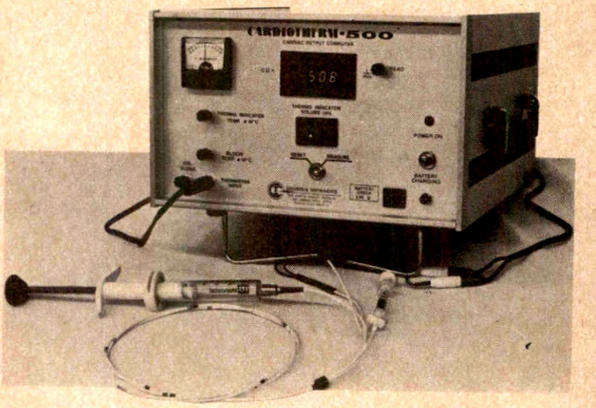

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Because the thiazides have a vital role at the start of antihypertensive therapy and as a part of later steps in therapy in combination with other agents, when necessary — consider DIURIL, the thiazide that started the thiazides.

Contraindications include anuria and hypersensitivity to chlorothiazide or other sulfonamide-derived drugs. Use with caution in patients with severe renal disease, impaired hepatic function, or progressive liver disease. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity.

Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy.

DIURIL...a long, impressive record in the management of hypertension

MSD
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For a brief summary of prescribing information, please see following page

...a long, impressive record in the management of hypertension

Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs; routine use in an otherwise healthy pregnant woman with or without mild edema.

Warnings: Use with caution in severe renal disease since thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.

Use in pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy or in women of childbearing potential, weigh anticipated benefit against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.

Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.

Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.

Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.

Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

How Supplied: Tablets containing 250 mg chlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 500 mg chlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100; Oral Suspension containing 250 mg chlorothiazide per 5 ml in bottles of 237 ml.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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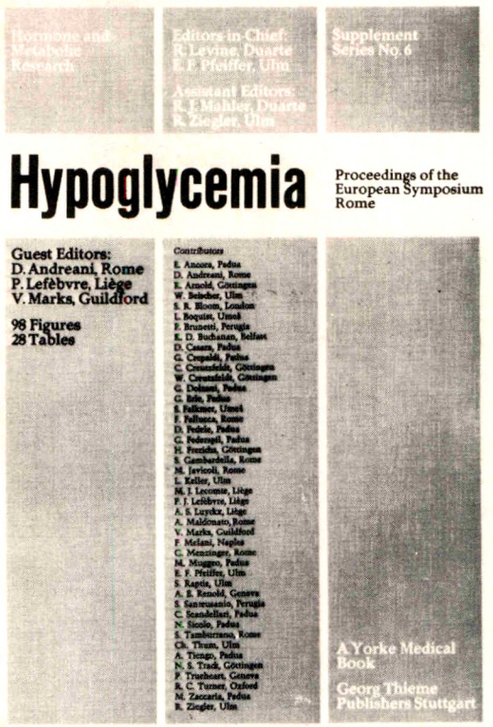
Hypoglycemia

new—just published

a widespread disease

an important subject



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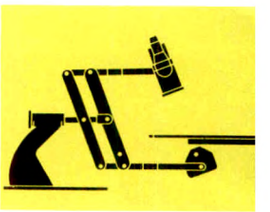

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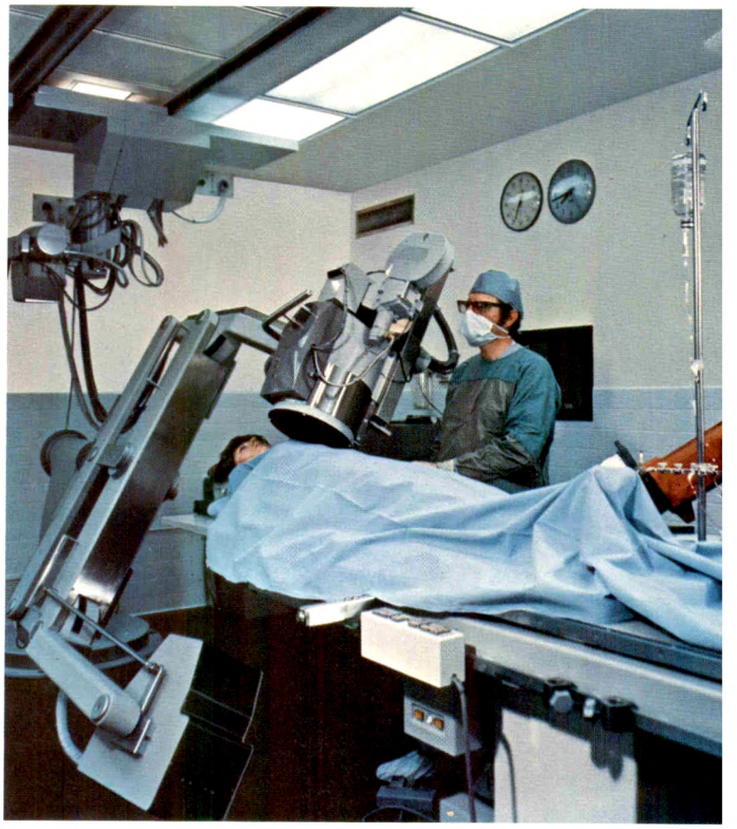
Philips Poly Diagnost C: new directions for improved cardiovascular diagnostics.



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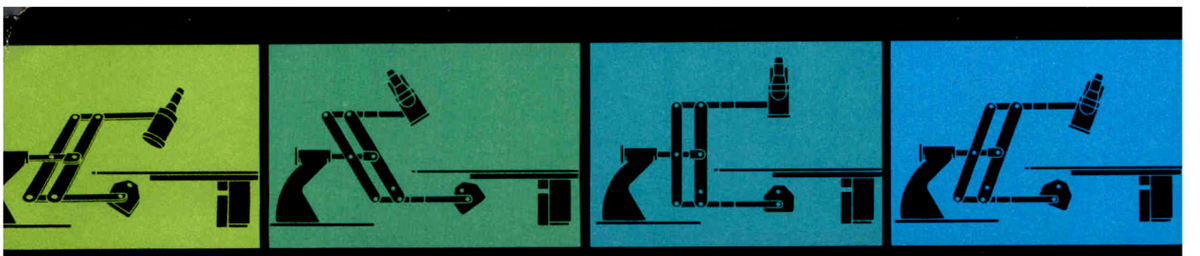

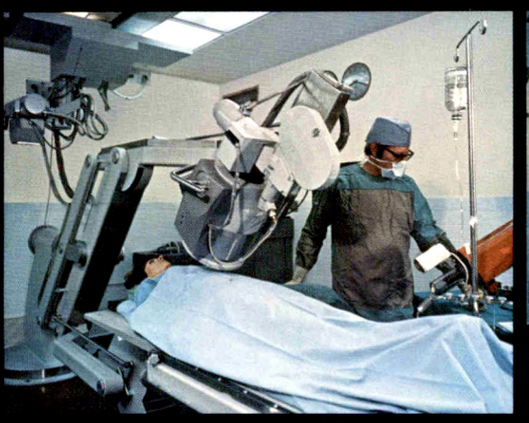

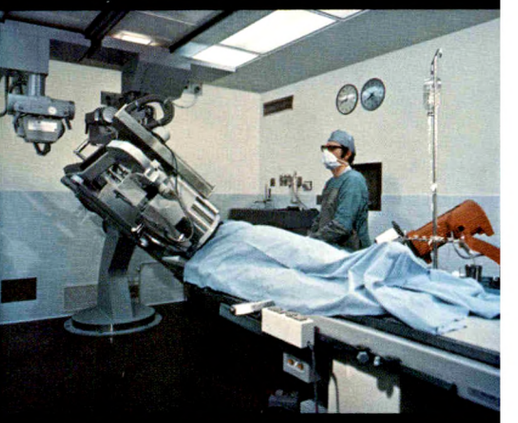

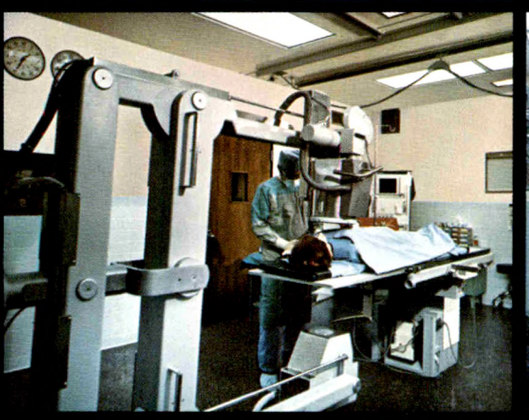

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*The drug has been evaluated as possibly effective for this indication.
See brief summary.

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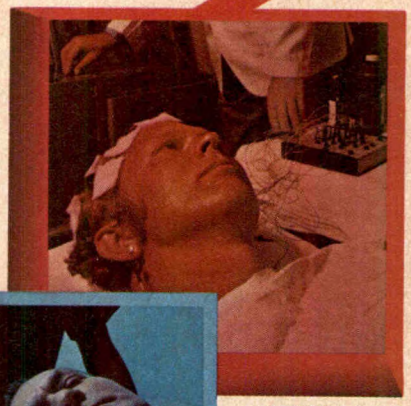
The versatility of
It's evident on almost

As a psychotherapeutic agent, Valium (diazepam) serves a wide range of needs

Whatever the patient's primary diagnosis, excessive anxiety sometimes becomes an important factor in treatment. In such cases, you'll find Valium an extremely useful adjunct to counseling. That's because oral Valium acts promptly and effectively to calm the tense, overreacting patient and to reduce his anxiety to more manageable levels. Moreover, Valium may be given to psychoneurotic patients whose predominant anxiety is accompanied by secondary depressive symptoms. And when anxiety is particularly acute—before surgery, endoscopy or cardioversion, for instance—Valium is available in injectable form to provide immediate calming.

Valium is generally well tolerated, with side effects more serious than drowsiness, fatigue and ataxia rarely seen. Ambulatory patients, however, should be cautioned against driving, operating dangerous machinery or drinking alcohol while on therapy with Valium.



NEUROLOGY

Valium (diazepam) serves as an adjunct in skeletal muscle spasm and spasticity

Because of its potent muscle-relaxant properties, Valium is a useful adjunct in relieving skeletal muscle spasm caused by sprains, strains or inflamed muscles. In such cases, adjunctive Valium often helps break the reflex cycle of spasm/pain/spasm and thus tends to increase mobility more rapidly. In certain other disorders as well—such as paraplegia and athetosis—rehabilitation specialists often find the spasmolytic action of Valium helpful in relieving involuntary movements, muscular rigidity and convulsive spasms. And you can choose from scored tablets or injectable dosage forms to suit an individual patient's needs.

Because of its relatively low toxicity, Valium has a noteworthy safety record. Nevertheless, as with any long-term drug therapy, periodic blood counts and liver function tests are advisable.

EMERGENCY ROOM

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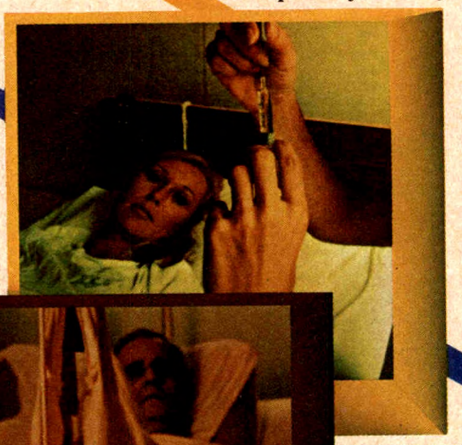
Valium® (diazepam) every hospital service

In status epilepticus particularly, Injectable Valium (diazepam) serves a vital need

Injectable Valium is now considered by many authorities to be a preferred drug in the management of status epilepticus. Used adjunctively, it generally succeeds in interrupting seizures promptly. Frequently, a single injection helps restore control. Injectable Valium has at times been effective even after standard anticonvulsants have failed.

If used intravenously, Injectable Valium should be administered slowly, taking at least one minute for each 5 mg (1 ml) given; it should not be mixed or diluted with other solutions or fluids. Although Injectable Valium seldom alters vital signs, because of the possible occurrence of apnea and/or cardiac arrest (especially in elderly or very ill patients), resuscitative facilities should be readily available. (See product information.)



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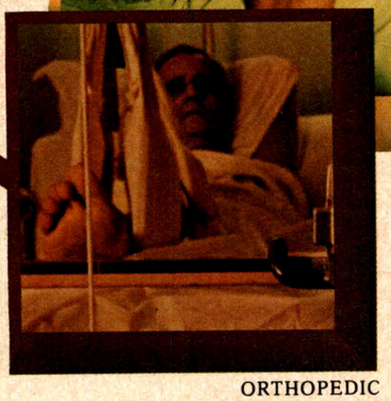

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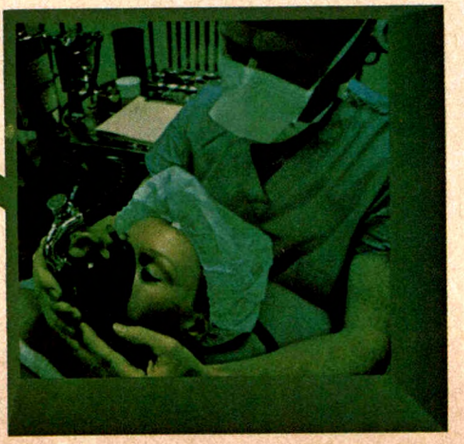

Valium® (diazepam) IV®

· few products on any hospital formulary do so much so well

For a summary of product information, please see following page.

Valium® (diazepam)

2-mg, 5-mg, 10-mg scored tablets
ready-to-use
2-ml Tel-E-Ject® (disposable syringes) } 5 mg/ml
2-ml ampuls
10-ml vials

three distinct actions: psychotherapeutic skeletal muscle relaxant anticonvulsant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome. *Oral form* may be used adjunctively in convulsive disorders, but not as sole therapy. *Injectable form* may also be used adjunctively in: status epilepticus; severe recurrent seizures; tetanus; anxiety, tension or acute stress reactions prior to endoscopic and surgical procedures; cardioversion.

Contraindications: Use of Injectable in infants and Tablets in children under 6 months of age; known hypersensitivity to drug; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, nursing women or in women of childbearing potential requires that expected benefit be weighed against possible hazard.

ORAL: Not of value in treatment of psychotic patients; should not be employed in lieu of appropriate treatment. When using oral form adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures.

INJECTABLE: *When used I.V., the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment. Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Administer with extreme care to elderly or very ill and those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; resuscitative facilities should be available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓ and administer in small increments. Not recommended for OB use until additional information is available. Should not be administered to patients in shock, coma or in acute alcoholic intoxication with depression of vital signs.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Limit oral dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

INJECTABLE: Laryngospasm and increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic and have necessary countermeasures available; hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly and debilitated; safety and efficacy in children under 12 not established.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue and ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium (diazepam) therapy and are of no known significance.

INJECTABLE: Venous thrombosis and phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.
In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat or chest have been reported.

Dosage: Individualized for maximum beneficial effect.

ORAL—*Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg *b.i.d.* to *q.i.d.*; acute alcohol withdrawal, 10 mg *t.i.d.* or *q.i.d.* in first 24 hours, then 5 mg *t.i.d.* or *q.i.d.* as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg *t.i.d.* or *q.i.d.*; adjunctively in convulsive disorders, 2 to 10 mg *b.i.d.* to *q.i.d. Geriatric or debilitated patients:* 2 to 2½ mg 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg *t.i.d.* or *q.i.d.* initially, increasing as needed and tolerated (not for use under 6 months).
INJECTABLE: Usual initial adult dose is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma and diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Immediate gastric lavage indicated for overdosage with tablets. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® (unit dose) packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam, compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

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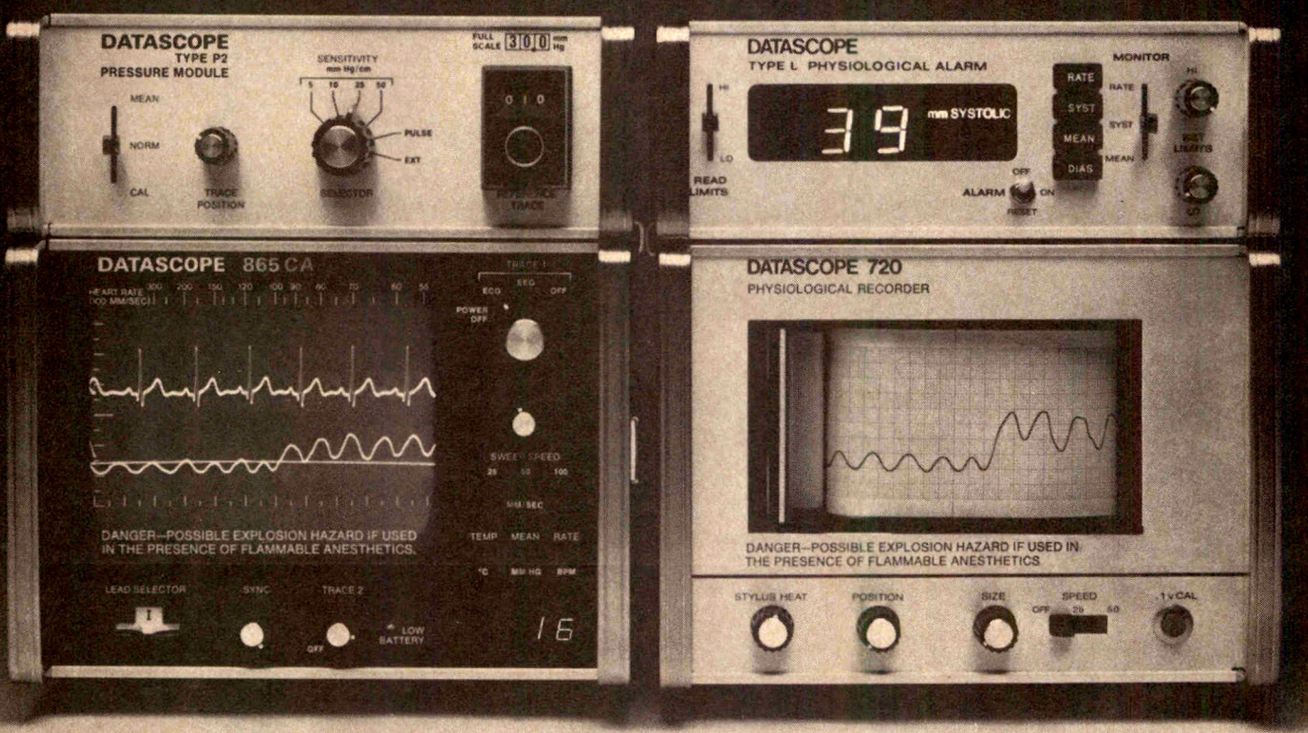

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Effect of Amiodarone in the Wolff-Parkinson-White Syndrome

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The effect of amiodarone in the Wolff-Parkinson-White syndrome was studied with programmed electrical stimulation of the heart in 15 patients. All 15 patients had circus movement tachycardias; 7 also had atrial fibrillation. Programmed electrical stimulation was performed before and after 14 days of oral administration of amiodarone. The effective refractory period of the accessory pathway lengthened in an atrioventricular direction in all patients and in a ventriculoatrial direction in eight patients. The effective refractory period of the atrium and ventricle lengthened in 14 and 12 patients, respectively. After administration of amiodarone, circus movement tachycardia could no longer be initiated in five patients. The zone of tachycardia narrowed in four patients, did not change in two and increased in seven. The effect of amiodarone on initiation of circus movement tachycardia could be related to differences in effect of the drug and in the mechanism of tachycardia in individual patients. In all patients in whom tachycardias could still be initiated after treatment with amiodarone the heart rate during tachycardia was slower than before treatment. This slowing was caused by a decrease in conduction velocity of the circulatory wave in different parts of the tachycardia circuit. The effect of amiodarone in prolonging the refractory period of the accessory pathway makes this drug especially useful in patients with the Wolff-Parkinson-White syndrome and atrial fibrillation.

Recently Rosenbaum et al.[1] reported on the beneficial effect of amiodarone hydrochloride in patients with the Wolff-Parkinson-White syndrome and tachycardias. In this report we describe the effect of this drug in similar patients, as studied with programmed electrical stimulation of the heart.

Material and Methods

Cases: Fifteen patients, 11 male and 4 female, with the Wolff-Parkinson-White (WPW) syndrome, were studied. Their ages ranged from 14 to 55 years. All patients had electrocardiographically documented attacks of regular tachycardia with a QRS configuration indicating atrioventricular (A-V) conduction over the A-V node. Seven patients also had atrial fibrillation. Twelve patients had type A WPW conduction and three had type B conduction.[2]

Procedures: After the patient's informed consent was obtained, at least four catheters were passed through the femoral veins using the Seldinger technique. Two bipolar catheters were positioned high on the lateral wall of the right atrium. One was used for stimulation, the other for recording an intraatrial electrogram. A bipolar catheter was placed in the region of the bundle of His to record an electrogram in this area.[3] A fourth (bipolar) catheter, positioned in the apex of the right ventricle, was used for ventricular stimulation. A fifth catheter was used to record a left atrial electrogram in seven patients; in five the catheter was passed into the left atrium through a patent foramen ovale and in the remaining two it was positioned in the coronary sinus.

Measurements: With use of the single test stimulus method during atrial stimulation the effective refractory periods of the accessory pathway, the A-V node (if shorter that that of the accessory pathway), the atrium and the zone of

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TABLE I. Summary of Measurements*

Case no.	Age (yr) & Sex	Type WPW	Cycle Length	ERP_{AP} A-V Direction Am−	ERP_{AP} A-V Direction Am+	ERP_{AP} A-V Direction Δ	ERP_{AP} V-A Direction Am−	ERP_{AP} V-A Direction Am+	ERP_{AP} V-A Direction Δ	ERP_{RA} Am−	ERP_{RA} Am+	ERP_{RA} Δ	ERP_{RV} Am−	ERP_{RV} Am+	ERP_{RV} Δ	Circus Movement Tachycardia Initiation Am−	Initiation Am+	Tachycardia Zone Am−	Tachycardia Zone Am+	R-R Am−	R-R Am+
1	22M	A	600	240	270	30	250	250	0	210	240	30	240	260	20	1APB 1VPB		240–210 310–250		320	
2	55M	A	600	240	310	70	320	320	0	230	300	70	260	280	20	1APB	1APB	240–230	310–250	380	460
3	46F	B	700	260	280	20	280	280	0	210	250	40	200	260	60	1APB	1APB	260–210	280–250		
4	38M	A	700	<270	470	⩾200	<230	370	⩾140	270	300	30	230	260	30	1VPB	1APB	430–230	490–260	340	470
5	22M	A	600	260	290	30	290	380	90	200	230	30	200	240	40	1APB		370–330 240–250	370–330	320	370
6	32M	A	600	<240	<300		260	260	0	240	300	60	220	240	20	1VPB	1VPB	260–240 280–220	360–240	320	400
7	30F	A	550	<230	290	⩾60	<220	220		230	230	0	220	210	−10	1VPB	1VPB	420–280	430–340	430	470
8	14F	B	450	300	350	50	250	250	0	250	270	20	220	240	20	1APB 1VPB	1APB 1VPB	300–250 290–260	350–270 290–260	360	410
9	22M	A	500	270	520	250	<220	520	⩾300	200	270	70	220	220	0	1APB		270–200		400	
10	19F	A	700	400	700	300	330	370	40	200	220	20	250	260	10	1APB	1APB	400–280	510–320	360	430
11	48M	A	700	310	460	150	<200	410	⩾210	260	290	30	200	240	40	1APB 1VPB	1APB 1VPB	290–260 320–200	370–360 310–250	360	410
12	21M	A	500	250	410	160	<240	300	⩾60	180	300	120	240	230	−10	1APB	1APB	250–210	410–300	285	370
13	39M	B	600	240	270	30	270	<270		220	260	40	240	270	30	1VPB		270–240		320	
14	19M	A	600	<200	<220	⩾40	<230	270	⩾40	200	220	20	230	260	30	1VPB		500–400		400	
15	52M	A	600	<230	330	⩾100	<240	290	⩾50	230	260	30	240	280	40	1VPB	1VPB	270–240	570–380	390	560

* All values in msec. Am− = before amiodarone; Am+ = after amiodarone; AP = accessory pathway; APB = atrial premature beat; A-V = atrioventricular; ERP = effective refractory period; RA = right atrium; RV = right ventricle; V-A = ventriculoatrial; VPB = ventricular premature beat; WPW = Wolff-Parkinson-White conduction.

premature beat intervals initiating tachycardia were carefully determined. Thereafter during single test stimulation of the right ventricle the pattern and effective refractory period of ventriculoatrial (V-A) conduction, the zone of premature beat intervals initiating tachycardia and the effective refractory period of the ventricle were measured. Previously described criteria[4] were applied to determine the pathways used during V-A conduction and reentrant tachycardia.

The same measurements using identical basic cycle lengths and test stimulus intervals were repeated after 14 days of oral administration of amiodarone. The drug was given in doses of 200 mg three times daily during the 1st week and 100 mg three times daily during the 2nd week. Whenever possible, the stimulating and recording electrodes were placed in the same position as during the first catheterization so as to minimize the effect of different approaches to the A-V node and accessory pathway on the function of these structures.[5–8] Stimulus strength during both catheterizations was kept at twice diastolic threshold.

All data obtained during the stimulation studies were recorded on tape (Ampex FR 1300) and directly registered on an eight channel Elema recorder. Leads I, II, III, V_1, V_6, the intracavitary right atrial lead, a left atrial lead if available and the His bundle lead were recorded simultaneously. For recording the His bundle electrogram an Elema EMT 12 was used.

Definitions: The effective refractory periods of the accessory pathway in the atrioventricular and ventriculoatrial directions were defined, respectively, as the longest A_1-A_2 interval failing to conduct over the accessory pathway and the longest V_1-V_2 interval failing to conduct over the accessory pathway. The effective refractory periods of the atrium and ventricle were defined, respectively, as the longest atrial test stimulus interval not followed by atrial depolarization and the longest ventricular test stimulus interval not followed by ventricular depolarization. The effective refractory period of the A-V node was defined as the longest A_1-A_2 interval failing to conduct through the A-V node. Statistical analyses were performed using the paired *t* test.

Results (Tables I and II)

A-V Conduction

The length of the effective refractory period of the accessory pathway increased in all patients, ranging from 200 to 400 msec before administration of amiodarone and from 220 to 700 msec after drug administration. In patients whose absolute values could be determined, the increase measured 109 ± 101 msec (mean ± 1 standard deviation).

TABLE II

Cumulative Data*

	Control	Amiodarone	Mean Change	*P* Value†
ERP_{AP} A-V direction	277 ± 50	386 ± 140	109 ± 101	<0.005
ERP_{RA}	220 ± 25	263 ± 30	40.7 ± 29	<0.01
ERP_{RV}	227 ± 18	250 ± 21	22.6 ± 17	<0.005
R-R circus movement tachycardia	359 ± 41	435 ± 57	80 ± 39	<0.005

* All measurements are expressed as mean ± standard deviation in msec.
† Paired *t* test.
Abbreviations as in Table I.

The effective refractory period of the A-V node before administration of amiodarone could be measured in only 4 patients (in 11 patients the effective refractory period of the accessory pathway was shorter than that of the A-V node or A-V conduction over the A-V node occurred up to the effective refractory period of the atrium). In these four patients the effective refractory period of the A-V node ranged from 210 to 280 msec before amiodarone; after amiodarone it could be measured in two of the four patients and had increased by 40 and 90 msec, respectively. In the other two patients the effective refractory period of the accessory pathway was shorter after amiodarone than the effective refractory period of the A-V node although it was still longer than the latter had been before drug administration.

The A-H interval during basic pacing of the atrium increased in all patients when the intervals were compared at identical basic cycle lengths before and after administration of amiodarone. The increase ranged from 15 to 35 msec (mean increase 23 ± 7 msec).

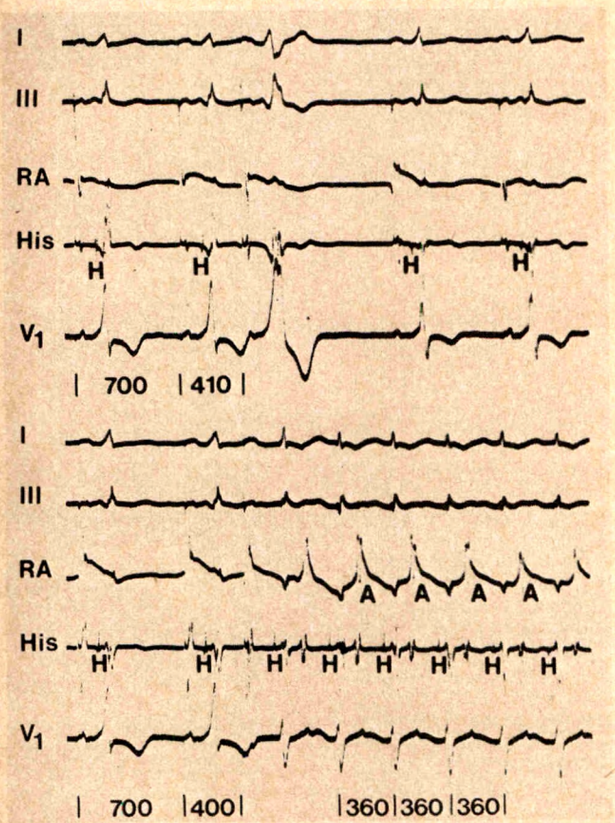
V-A Conduction

Application of criteria previously described[4] revealed that in all patients V-A conduction occurred over the accessory pathway up to the refractory period of the V-A conduction system. Administration of amiodarone lengthened the effective refractory period of the V-A conduction system in eight patients (by at least 40 to 300 msec). No change was observed in the remaining seven. The number of patients whose absolute values could be measured was too small to determine statistical significance.

In four of the eight patients with lengthening of the effective refractory period of the accessory pathway, V-A conduction still occurred over the accessory pathway. In the remaining four the A-V node became the pathway with the shortest effective refractory period in a V-A direction.

Atrium and Ventricle

The effective refractory period of the right atrium increased in 14 of the 15 patients. Before amiodarone,



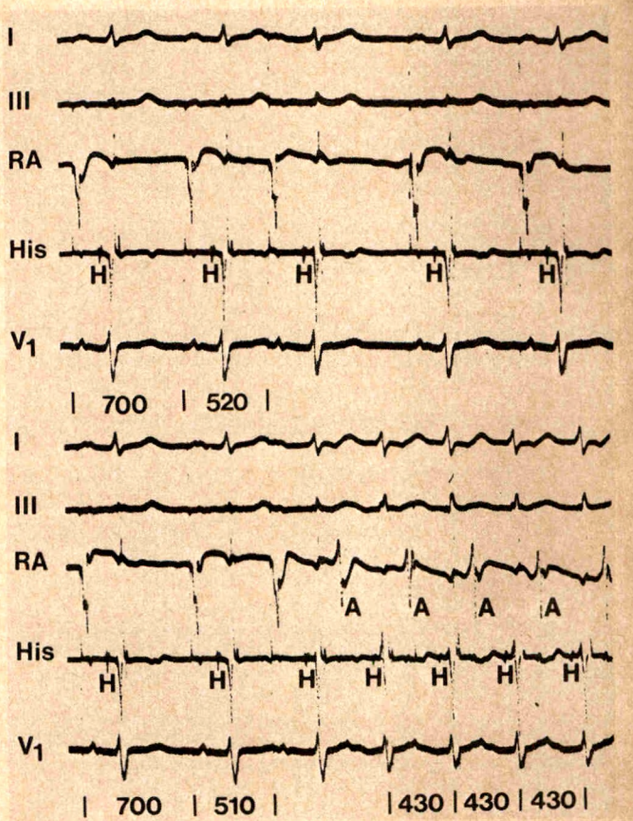


FIGURE 1 (left). Case 10. Before administration of amiodarone. **Upper panel,** during atrial pacing with a basic cycle length of 700 msec, A-V conduction over the accessory pathway occurs up to an atrial test stimulus interval of 410 msec. **Lower panel,** an atrial test stimulus given after 400 msec is conducted to the ventricle exclusively over the A-V node, initiating a tachycardia. A tachycardia could be initiated by a single atrial test stimulus up to the effective refractory period of the A-V node (280 msec). The R-R interval during tachycardia measures 360 msec.

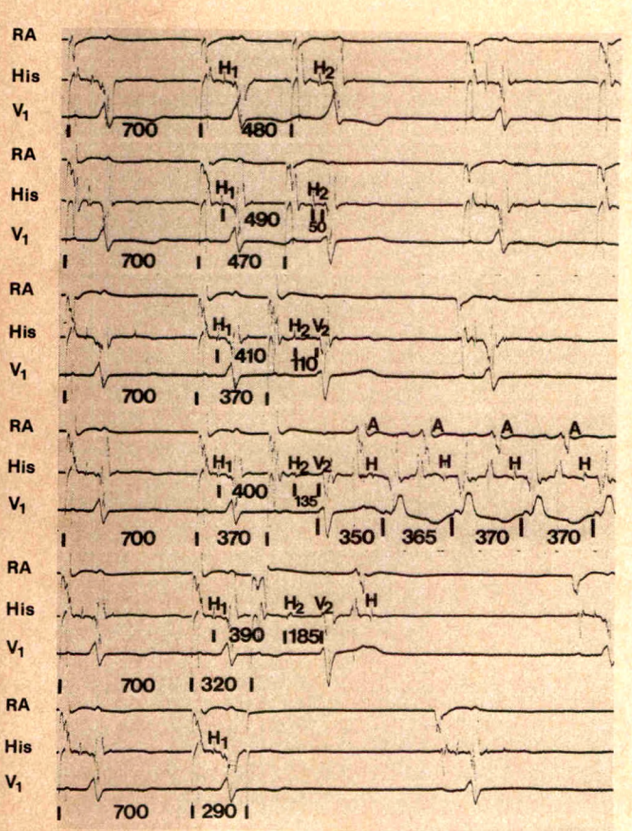
FIGURE 2 (right). Case 10. During administration of amiodarone. **Upper panel,** during atrial pacing with a basic cycle length of 700 msec complete block is present in the accessory pathway in an A-V direction. **Lower panel,** an atrial test stimulus given after 510 msec initiates a tachycardia. A tachycardia could be initiated by an atrial test stimulus up to the refractory period of the A-V node (320 msec). Comparison with Figure 1 reveals: (1) a wider zone of tachycardia after amiodarone (510 to 320 = 190 msec versus 400 to 280 = 120 msec); (2) a slower heart rate during tachycardia with amiodarone (R-R interval 360 msec before and 430 msec during drug administration). Higher speed recordings revealed that the increase in R-R interval was caused by lengthening of the A-H and V-A intervals. Ventricular pacing revealed that the effective refractory period of the accessory pathway in a V-A direction had not been affected by amiodarone.

values ranged from 180 to 270 msec and after amiodarone from 220 to 300 msec (mean increase 40.7 ± 9 msec); no change occurred in the remaining patient.

The effective refractory period of the right ventricle increased in 12 patients. Before amiodarone it was 200 to 260 msec; after amiodarone 240 to 280 msec (mean increase 22.6 ± 17 msec). No change was seen in one patient, and shortening by 10 msec occurred in the remaining two patients.

Mechanism of Tachycardia

Circus movement tachycardias: Before drug administration, circus movement tachycardias could be initiated with a single test stimulus in all patients; in five patients they could be initiated with an atrial premature beat, in six with a ventricular premature beat and in four with either a single atrial or a single ventricular premature beat. After administration of amiodarone, tachycardias could still be initiated with a single test



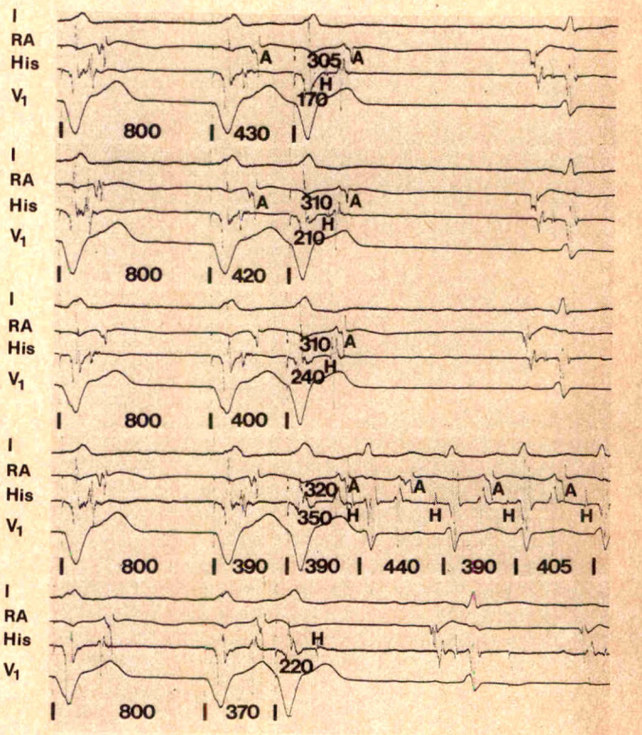


FIGURE 3 (left). Case 4. During administration of amiodarone. Six atrial test stimulus intervals are shown during atrial pacing with a basic cycle length of 700 msec in a patient with Wolff-Parkinson-White syndrome, type A. The **top panel** shows an atrial premature beat given after 480 msec resulting in more preexcitation as compared with the QRS complexes during basic pacing. The **second panel** reveals that the refractory period of the accessory pathway measures 470 msec. The H_2-V_2 interval measures 50 msec. The **third panel** shows prolongation of the H_2-V_2 interval to 110 msec with loss of voltage and widening of the His bundle electrogram after an atrial test stimulus given after 370 msec. The **fourth panel** at the same atrial test stimulus interval reveals further prolongation of the H_2-V_2 interval (to 135 msec) followed by tachycardia with A-V conduction over the A-V node and complete right bundle branch block. Study of the effect of ventricular premature beats during tachycardia revealed that V-A conduction occurred over the accessory pathway.[4] This mechanism of initiation of tachycardia (critical H_2-V_2 prolongation allowing recovery of the ventricular end of the accessory pathway) was present up to an atrial test stimulus interval of 330 msec. In the **fifth panel,** at an atrial test stimulus interval of 320 msec, there is further lengthening of the H_2-V_2 interval to 185 msec. After ventricular activation the impulse is conducted in retrograde fashion to the atrium over the accessory pathway, to reenter and traverse the A-V node. However, block occurs distal to the electrogram of the bundle of His and no tachycardia is initiated. Apparently slow conduction through the peripheral conduction system after the atrial premature beat (H_2-V_2 interval of 185 msec) makes the area distal to the bundle of His refractory to propagation of the next atrial impulse. The phenomenon shown in the fifth panel was present up to the effective refractory period of the atrium (**sixth panel**).

FIGURE 4 (right). Case 11. Events during single test stimulation of the right ventricle in a patient with the Wolff-Parkinson-White syndrome type A receiving amiodarone. In the **first three panels** a test pulse given with increasing prematurity is conducted to the atrium over the accessory pathway (demonstrated by the retrograde His bundle electrogram moving toward retrograde atrial activation). The number under the right atrial (RA) lead indicates the V-A conduction time of the test stimulus. The number under the His bundle lead gives the interval between the test stimulus and retrograde activation of the His bundle. The **fourth panel** shows V-A block in the ventriculo-His pathway, exclusive V-A conduction over the accessory pathway followed by a circus movement tachycardia. The **fifth panel** shows V-A block in the accessory pathway and in the A-V node. However, the His bundle is activated in retrograde manner, indicating (between strip 4 and 5) a gap in ventriculo-His bundle conduction. Before administration of amiodarone, V-A conduction over the accessory pathway had been present up to the effective refractory period of the accessory pathway.

stimulus in 10 patients, in three with either a single atrial or a single ventricular premature beat. Therefore the effect of amiodarone could be observed on 13 zones of tachycardia. In all these patients the interval of the earliest premature beat able to initiate tachycardia lengthened. In seven patients the zone of premature beats during which a tachycardia could be initiated (zone of tachycardia) widened (by 30 to 160 msec). In two patients this zone was unchanged (only shifted to longer premature beat intervals) and in four patients it shortened (by 20 to 60 msec).

In three patients ability to initiate tachycardia with a single atrial premature beat persisted in spite of considerable lengthening of the effective refractory period of the accessory pathway in an A-V direction (Fig. 1 and 2). A study of the effect of drug administration on V-A conduction during ventricular pacing provided the explanation. In two patients the effective refractory period of the accessory pathway in a V-A direction was unchanged; in the third it increased only 40 msec. In another patient in whom tachycardia could be initiated with a single ventricular premature beat before amiodarone, tachycardia was initiated after amiodarone only during atrial pacing (Fig. 3). The explanation was marked prolongation of the H-V interval, indicating slow conduction in the distal conduction system enabling recovery of the ventricular end of the accessory pathway. In spite of considerable lengthening of the effective refractory period of the accessory pathway in a V-A direction, initiation of tachycardia was still possible in another patient through ventricular or A-V nodal reentry (Fig. 4 and 5).

All 10 patients in whom a tachycardia could still be initiated showed a slower heart rate during tachycardia than before drug administration. The R-R interval during tachycardia, measuring 285 to 430 msec before administration of amiodarone, lengthened to 370 to 560 msec (mean increase 90 ± 42 msec). In all 10 patients the A-H interval lengthened during tachycardia (by 30 to 70 msec) and in 8 patients the V-A interval also lengthened (by 20 to 50 msec). An increase of 10 to 20 msec was noted in the H-V interval in four patients and in the width of the QRS complex in four patients.

Atrial fibrillation: Seven patients had electrocardiographically documented episodes of atrial fibrillation. In all seven patients atrial fibrillation was deliberately induced by rapid atrial pacing (400 to 500/min) before and after the administration of amiodarone. The mean ventricular rate during atrial fibrillation (mean of 12 consecutive R-R intervals) ranged from 180 to 270 beats/min before drug administration and decreased in all patients to 130 to 240 beats/min after amiodarone.

Discussion

Amiodarone hydrochloride, a benzfuran derivative with antagonistic effect on sympathetic nerve stimulation, has been reported to exert a beneficial effect in patients with angina pectoris[9,10] and cardiac arrhythmias.[11] The antiarrhythmic action of the drug has been attributed to its action increasing the duration of the action potential without affecting resting potential or maximal rate of depolarization of the action potential.[12] Rosenbaum et al.[1] described beneficial effects of amiodarone in patients with the Wolff-Parkinson-White syndrome who had arrhythmias. They reported that this was the result of lengthening of the refractory period of the accessory pathway, A-V node and His-Purkinje system.

The effect of various drugs on the Wolff-Parkinson-White syndrome has been studied with intravenous administration of these agents during cardiac pacing.[13–19] Since amiodarone is usually given orally we decided to study its effect on this syndrome by comparing data from programmed electrical stimulation of the heart before and after the drug had been administered orally for 14 days. Amiodarone resulted in lengthening of the effective refractory period of the accessory pathway. But, as with other drugs,[16] its effect on the accessory pathway was not similar when antegrade and retrograde conduction were compared. Whereas amiodarone uniformly prolonged refractoriness of the accessory pathway in an A-V direction, prolongation in a V-A direction was observed in only eight patients.

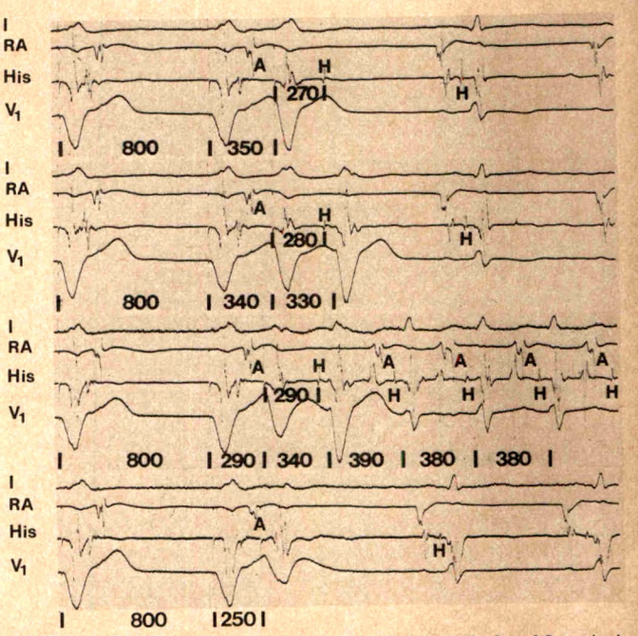


FIGURE 5. Case 11 (continued from Figure 4). In **panels 1 and 2** gradual prolongation of the ventriculo-His interval occurs after test stimuli given with increasing prematurity. A test stimulus given after 340 msec **(panel 2)** is followed by another QRS complex preceded by His bundle activation. This QRS complex is either the result of reentry at the ventricular level or reentry in the A-V node with left bundle branch block toward the ventricle. No V-A conduction follows this reentrant QRS complex. However, in the third panel, at shorter test stimulus intervals V-A conduction over the accessory pathway followed the reentrant beat, initiating tachycardia. The relation between atrial, His bundle and ventricular activation during the tachycardia is similar to that shown in Figure 4, panel 4. The mechanism of tachycardia shown in **panel 3** was present up to the effective refractory period of the ventriculo-His conduction system **(panel 4).**

Like Rosenbaum et al.[1] and Touboul et al.,[20] we found that amiodarone lengthened the refractory period of the A-V node, the A-H interval and usually also the refractory period of the atrium and ventricle. In some of our patients there was also prolongation of the H-V interval, indicating slowing of conduction in the specialized conduction system distal to the A-V node.

Mechanism of amiodarone effects on circus movement tachycardias: The effect of amiodarone on circus movement tachycardias with A-V conduction over the A-V node and V-A conduction over the accessory pathway varied individually. This was the result of different mechanisms: (1) Amiodarone had dissimilar effects on refractoriness of the accessory pathway in the A-V and V-A directions (Fig. 1 and 2). This finding confirms a previous observation[16] that the effect of a drug on circus movement tachycardia in the Wolff-Parkinson-White syndrome cannot be predicted from its effect on the accessory pathway during atrial pacing. (2) Although prolongation of the refractory period of the accessory pathway in a V-A direction after amiodarone could be demonstrated, concomitant slowing in the A-V nodal conduction system resulted in delayed arrival of the atrial impulse in the ventricle at a time when the ventricular end of the accessory pathway had recovered. The interplay between prolongation of the length of the refractory period of different constituents of the tachycardia circuit and slowing of conduction of the circulating impulse led in some patients to widening of the zone of tachycardia and shortening or no change in the width of this zone in others. (3) New mechanisms of initiation of tachycardia occurred, such as slowing of conduction in the subnodal conduction system (Fig. 3) or initiation of tachycardia after ventricular or A-V nodal reentry (Fig. 4 and 5). Since no blood levels of amiodarone were determined, individual differences in these levels may have also played a role in the effect of the drug on circus movement tachycardia.

In all our patients heart rate during tachycardia was much slower during amiodarone therapy than before drug administration. This was the result of slowing of conduction of the circulating impulse in different parts of the tachycardia pathway.

Clinical implications: Rosenbaum et al.[1] found a beneficial effect of amiodarone in patients with the Wolff-Parkinson-White syndrome and atrial fibrillation and in those with circus movement tachycardia. Our data from programmed electrical stimulation support the use of the drug in atrial fibrillation. During our study the effect of amiodarone on circus movement tachycardia varied in individual patients. However, programmed electrical stimulation of the heart provides the premature beat necessary to initiate tachycardia. Prevention of premature beats after administration of amiodarone might result in a favorable effect of the drug on circus movement tachycardia as well.

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Efficacy of Cardioselective Beta Adrenergic Blockade With Intravenously Administered Tolamolol in the Treatment of Cardiac Arrhythmias

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The efficacy of tolamolol, a cardioselective beta adrenergic blocking agent, was evaluated in the treatment of cardiac arrhythmias in 27 patients. Nineteen patients had supraventricular arrhythmias and eight had ventricular arrhythmias. Evaluation was by double-blind randomized trial in 23 patients. Tolamolol was effective in reducing ventricular rate in 17 (85 percent) of 19 patients with supraventricular arrhythmias and resulted in conversion to sinus rhythm in 2 of the 17. The mean ventricular rate in 17 patients decreased from 135 to 102/min 10 minutes after initiation of administration of tolamolol and gradually decreased further to 93/min after 60 minutes. Reduction in ventricular rate was sustained for 2 hours of monitoring undergone by all patients and for 4 and 6 hours monitoring in two subgroups. Among the eight patients with ventricular ectopic beats, tolamolol reduced their frequency in four patients and had no effect in four. Six patients had chronic obstructive pulmonary disease and experienced no adverse clinical effects on respiratory function in association with administration of tolamolol. Untoward effects occurred in 10 patients, including hypotension in 3, 1 of whom required vasopressor therapy. Other side effects were sedation, nausea, dyspnea and warmth in the chest, all of which were mild and transient, requiring no treatment.

Cardioselective beta adrenergic blockade with tolamolol was highly effective in controlling ventricular rate in supraventricular arrhythmias and reduced the frequency of ventricular ectopic beats in half of the small group of patients with this arrhythmia. It is particularly applicable in patients with obstructive pulmonary disease in whom cardiac beta adrenergic blockade is indicated. Hypotension is an important potential side effect.

The efficacy of beta adrenergic blocking agents has been demonstrated in the treatment of a variety of cardiac arrhythmias.[1–9] Most clinical experience with this class of compounds pertains to propranolol which, although generally useful, is limited or contraindicated in certain conditions.[3,5,6,9–11] The development of beta adrenergic blocking agents with specificity for the subcategories of beta receptors, and thereby with tissue selectivity, has broadened the indications and increased the applicability of this form of therapy. Tolamolol is a recently introduced phenoxypropranolamine derivative that preferentially inhibits myocardial beta adrenoreceptors,[6,12–15] possesses beta blocking potency equivalent to propranolol,[6,13–16] has little or no direct cell membrane effects[6] and lacks beta adrenergic stimulating action.[6,13,16] This study evaluated the efficacy of intravenously administered tolamolol* in the treatment of cardiac arrhythmias of atrial and ventricular origin in man.

Methods and Materials

The study group consisted of 28 hospitalized patients, 18 men and 10 women, with a mean age of 64 years (range 50 to 83). Twenty patients had supraventricular tachyarrhythmias, and eight were treated for ventricular arrhythmias.

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* Kindly supplied for investigation by Colin Taylor, MD of Pfizer, Inc., Groton, Conn.

The supraventricular arrhythmias consisted of atrial fibrillation (16 patients), multifocal atrial tachycardia (2 patients) and atrial flutter (2 patients). The ventricular arrhythmias included ventricular ectopic beats in all eight patients and salvos of three to four consecutive beats in one of the eight. Primary diagnoses in the patients with supraventricular tachyarrhythmias were chronic obstructive pulmonary disease (six patients), rheumatic valvular heart disease (four patients), chronic ischemic heart disease (four patients), atrial septal defect (one patient), pneumonia (two patients), postcardiac surgery arrhythmia (one patient) and cardiomyopathy (one patient); in one patient with supraventricular tachyarrhythmia no underlying cardiac or systemic disease was evident. Diagnoses in the group with ventricular arrhythmias included chronic ischemic heart disease (three patients), rheumatic valvular heart disease (three patients) and cardiomyopathy (one patient); in one patient no underlying cause was evident.

In the 20 patients with supraventricular tachyarrhythmias the ventricular rate was 110/min or greater (mean 136/min, range 110 to 200). In the group with ventricular arrhythmias, ventricular ectopic beats occurred at a frequency of 5 or more/min in all patients (mean frequency 24/min, range 5 to 46/min), were multifocal in four patients and paired in five patients. In the single patient with salvos of ectopic beats this phenomenon occurred 10 times/min.

Electrocardiographic data: Persistence of the arrhythmia for at least 30 minutes before the onset of treatment was documented in all patients. All electrocardiographic data were obtained by continuous monitoring on electromagnetic tape with a portable electrocardiographic recorder (Avionics model 385 or 400). Continuous monitoring was performed for 30 minutes before drug administration and for up to 6 hours thereafter. The tapes were analyzed on an electroscanner (Avionics model 350) at a ratio of scanning speed to real time of 60:1. Electrocardiographic recordings for determination of cardiac rhythm and rate were made from the tapes when any change in rhythm occurred and, in addition, at 5 minute intervals before and during drug administration and at 10 and 30 minutes and 1 hour intervals after completion of administration. Each recording was at least 1 full minute, or for as long as required to record an actively changing rate or rhythm. At each data point, the ventricular rate in the patients with supraventricular tachyarrhythmias and the frequency of ventricular ectopic beats in the patients with ventricular arrhythmias were determined by direct counting of the full minute recordings. During scanning of the tapes, calculation (by averaging of ventricular rate and summation of total number of ventricular ectopic beats) of these same data for periods of 5 to 15 consecutive minutes which encompassed each of the data points demonstrated no differences in the information provided by the selected recording points and the associated larger intervals.

Drug administration protocol: Administration of medication was by double-blind trial of tolamolol and placebo in 15 of the 20 patients with supraventricular tachyarrhythmias and 6 of the 8 patients with ventricular arrhythmias. Five of the former patients and two of the latter received tolamolol by open administration without placebo trial. The trial protocol consisted of consecutive intravenous administration of tolamolol and placebo (saline solution) in double-blind, randomized fashion, each over a 30 minute period. The two agents were obtained from coded vials for later identification. The maximal dose of tolamolol was 20 mg. Total volume of each agent was 10 ml, and administration was by incrementally increasing volumes, so that tolamolol was given in the following manner: 0 minute 1 mg, 5 minutes 2 mg, 10 minutes 2 mg, 15 minutes 3 mg, 20 minutes 3 mg, 25 minutes 4 mg, 30 minutes 5 mg (total 20 mg). If there was no significant effect within 40 minutes after initiation of therapy with the first agent, the second agent was given according to the same procedure. The same method of administration was employed in the patients who received tolamolol openly. Drug administration was discontinued at any point in the sequence if a satisfactory therapeutic effect on cardiac rhythm was obtained or if untoward signs or symptoms occurred.

All data were analyzed without knowledge of their relation to placebo or tolamolol therapy.

Results

Supraventricular Tachyarrhythmias

Tolamolol was effective in 17 (85 percent) of the 19 patients who received it for supraventricular tachyarrhythmias. The therapeutic effect consisted of reduction of ventricular rate in 15 patients and conversion to normal sinus rhythm in 2 patients (Table I). Tolamolol had no beneficial effect in two patients (11 percent), one with atrial fibrillation and one with multifocal atrial tachycardia. One patient did not receive tolamolol because conversion from atrial fibrillation to normal sinus rhythm occurred during prior placebo administration. Placebo was without effect in the other 9 of the 15 patients in the double-blind trial who received it. Five of the 15 patients in the double-blind trial did not receive placebo since tolamolol, the first agent given them, produced a therapeutic response. The total dose of tolamolol given was 20 mg in 10 patients, 15 mg in 1 patient, 11 mg in 2 patients, 8 mg in 3 patients and 5 mg in 3 patients.

The two patients who manifested conversion to normal sinus rhythm with tolamolol had atrial fibrillation and atrial flutter, respectively. The mean ventricular rate in the responsive group of 17 patients decreased abruptly from 135/min to 102/min 10 minutes after initiation of tolamolol therapy and progressively decreased further to 93/min at 60 minutes after the onset

TABLE I
Summary of 28 Cases

	Tolamolol Therapy	Tolamolol Benefit	Tolamolol Failure
Supraventricular Arrhythmias (20 patients)			
Number of patients	19*	17 (89%)	2 (11%)
Percent decrease in ventricular rate in responders†		35 (13 to 55)	
Conversion to normal sinus rhythm		2 of 19 (11%)	
Ventricular Arrhythmias (8 patients)			
Number of patients	8	4 (50%)	4 (50%)
Percent decrease in ventricular ectopic beats/min in responders†		98 (93–100)	

* In 1 of the 20 patients atrial fibrillation was converted to normal sinus rhythm during placebo administration; this patient therefore did not receive tolamolol.

† Maximal effect.

of therapy (Fig. 1). Reduction in the ventricular rate was sustained for the 2 hour monitoring period undergone by the entire group and throughout the 4 and 6 hour intervals during which recording was continued in two subgroups (11 and 8 patients, respectively) (Fig. 1). Figure 2 illustrates the response to tolamolol in a patient with atrial fibrillation and Figure 3 in a patient with atrial flutter. The mean maximal reduction of ventricular rate was 35 percent (13 to 55 percent) in the responsive group (Table I), and the maximal reduction was 23 percent or more in 14 of the 17 patients (82 percent). This maximal reduction occurred within 30 minutes or less of tolamolol administration in 14 patients. The reduction of ventricular rate after administration of tolamolol persisted for 2 or more hours after completion of drug administration in 15 of the 17 patients and was of 30 and 60 minutes' duration in the remaining 2.

Ventricular Arrhythmias

Tolamolol therapy was effective in four (50 percent) of the eight patients with ventricular arrhythmias (Table I). Placebo had no effect on these arrhythmias in any of the five patients receiving it, and tolamolol was without effect in four patients (50 percent) (Table I). The total dose of tolamolol was 20 mg in seven patients and 5 mg in one patient.

In the four patients who responded to tolamolol, the mean frequency of ventricular ectopic beats decreased relatively rapidly and progressively, reaching a minimum at 2 hours that persisted at 6 hours (Fig. 4); the maximal decrease in frequency was 100 percent in each of the four patients. Two of the four patients had multifocal ventricular ectopic beats, and one had paired ectopic beats before administration of tolamolol, all of which were abolished after the drug was given. In the patient with frequent salvos of ventricular ectopic beats, complete suppression was achieved. There was no relation between type of underlying heart disease and response to tolamolol.

The time course of the response to tolamolol was very similar in the patients with supraventricular tachyarrhythmias and in those with ventricular ectopic beats who responded to the drug (Fig. 1 and 4).

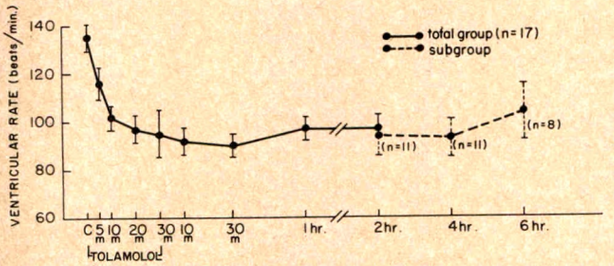

FIGURE 1. Ventricular rate before (C) and after intravenous administration of tolamolol in the 17 patients with supraventricular tachyarrhythmias with effective response. Evaluation was carried out for 2 hours in the entire group and for 4 and 6 hours for subgroups of 11 and 8 patients, respectively. Tolamolol was administered during the first 30 minute period. Times after the first 30 minutes refer to interval after completion of tolamolol administration. Data are indicated as mean ± standard error of the mean. hr. = hours; m = minutes.

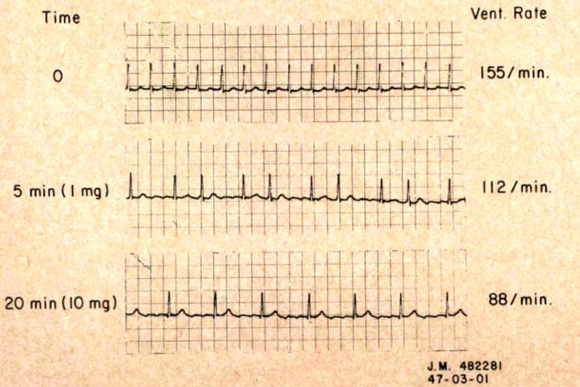

FIGURE 3. Serial electrocardiograms after intravenous administration of tolamolol in a patient with atrial flutter. The cumulative dose of tolamolol is indicated in parentheses at each time period.

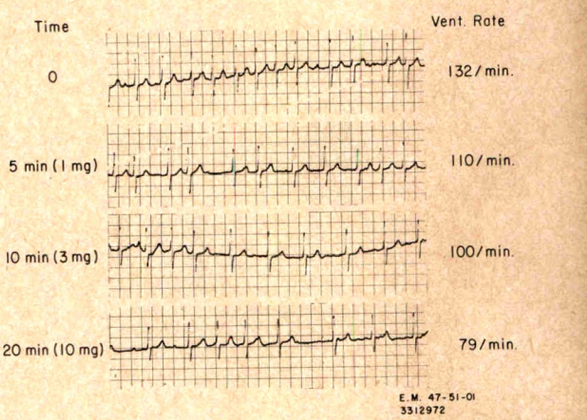

FIGURE 2. Serial electrocardiograms after intravenous administration of tolamolol in a patient with atrial fibrillation. The cumulative dose of tolamolol is indicated in parentheses at each time period. Vent. = ventricular.

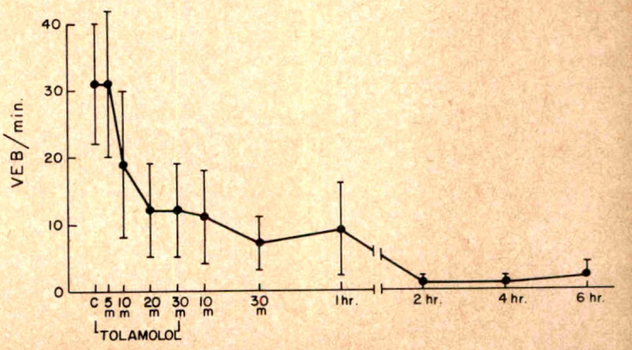

FIGURE 4. Frequency of ventricular ectopic beats (VEB) before (C) and after intravenous administration of tolamolol in four patients with a therapeutic response. Tolamolol was administered during the first 30 minute period. Times after the first 30 minutes refer to interval after completion of tolamolol administration. Data are indicated as mean ± standard error of the mean. hr. = hours; m = minutes.

Untoward Effects

A total of 11 untoward effects occurred in 10 patients in association with tolamolol therapy. These included hypotension (three patients), defined as a decrease in systolic blood pressure of 30 mm Hg or more or a reduction of this pressure to less than 100 mm Hg; a warm feeling in the chest (five patients); sedation (one patient); nausea (one patient); and dyspnea (one patient). The warm sensation in the chest was not associated with symptoms of pressure, constriction or other evidence of angina pectoris. This symptom and the latter three reactions were mild and transient and did not require alteration of drug administration. All three patients with hypotension had supraventricular tachyarrhythmias, and a significant reduction of ventricular rate had been achieved at the time of the reduction in blood pressure, which was transient in two patients, reverting to normotensive levels without specific therapy.

In the third patient with hypotension, l-norepinephrine infusion was required. This patient was a 60 year old acutely and chronically ill man who had presented the previous day with pneumonia in the right middle and lower pulmonary lobes, symptoms of alcohol withdrawal and atrial fibrillation with a ventricular rate of 180/min. He also had chronic obstructive pulmonary disease, lymphoma and macrocytic anemia. When he received tolamolol on the 2nd hospital day he was comatose, had undergone endotracheal intubation and was requiring mechanical ventilatory assistance consequent to respiratory and cardiac arrests on the previous day. He had atrial fibrillation with a ventricular rate of 200/min that was unresponsive to direct current countershock, digitalis and quinidine. Systolic blood pressure ranged from 76 to 100 mm Hg. Immediately before administration of tolamolol, the ventricular rate was 200/min and blood pressure 100/70 mm Hg. After 1 mg of tolamolol, the ventricular rate decreased to 175/min and blood pressure increased to 110/80 mm Hg. After an additional 2 mg of tolamolol the ventricular rate was 200/min and blood pressure 90/60 mm Hg. Administration of 2 mg more of the drug was followed after 4 minutes by a reduction in ventricular rate to 140/min, but systolic blood pressure decreased to 70 mm Hg. Infusion of l-norepinephrine immediately restored blood pressure to 120/90 mm Hg. Vasopressor therapy was progressively decreased and completely discontinued after 4 hours, but the patient remained comatose with no improvement and died 24 hours later after recurrent ventricular arrhythmias, hypotension and two cardiac arrests.

Discussion

Tolamolol was consistently and rapidly effective in reducing the elevated ventricular rate in patients with supraventricular tachyarrhythmias. It was less reliable in the treatment of ventricular arrhythmias, but successfully suppressed them in half of the small group of patients who received it for this indication. The arrhythmias responding to tolamolol were related to a wide variety of underlying diagnoses, suggesting the broad applicability of the agent. These conclusions regarding the therapeutic efficacy of tolamolol are supported by the controlled, objective method of evaluation used in this study.

Electrophysiologic effects: The antiarrhythmic effect of tolamolol is attributable to its myocardial $beta_1$ adrenergic blocking action, since the agent has little local anesthetic or quinidine-like effect on cellular transmembrane potentials.[6] Cardiac beta adrenergic blockade antagonizes the actions of intrinsic or extrinsic sympathetic stimulation of the heart, resulting in delayed conduction velocity and increased refractory period in the atrioventricular (A-V) node and decreased automaticity of myocardial cells,[1,3,5,6,9] effects that are potentially beneficial in a variety of arrhythmias of supraventricular and ventricular origin. The reduction of ventricular rate by tolamolol in supraventricular arrhythmias is closely related to its prolongation of the refractory period and delay of conduction in the A-V node, resulting in a decrease in the number of impulses reaching the ventricles. Blockade of cardiac beta receptors is beneficial in those ventricular arrhythmias related to augmented sympathetic neurohumoral stimulation of the myocardium.[1,3,5–7,9]

Clinical experiences: The effectiveness of tolamolol in our patients confirms preliminary experience with this agent.[17,18] These earlier studies also demonstrated greater efficacy of intravenously administered tolamolol in the treatment of supraventricular than ventricular arrhythmias. Further, in these studies, in the great majority of patients with atrial fibrillation and flutter, the therapeutic effect consisted of reduction of ventricular rate and, as in our experience, conversion to sinus rhythm was unusual. In digitalis-induced arrhythmias, whether supraventricular or ventricular, a high rate of success with tolamolol was noted[17,18] and preliminary data[18] indicated that orally administered tolamolol was beneficial in the treatment of cardiac arrhythmias in ambulatory patients.

Further evidence of the efficacy of cardioselective beta adrenergic inhibition in the treatment of cardiac arrhythmias is afforded by experience with practolol, another $beta_1$ adrenoreceptor blocking agent. In its application by our group[4] and others,[2,5–8] practolol has had a relatively consistent action of effectively reducing excessive ventricular rate in supraventricular tachyarrhythmias associated with acute ischemic heart disease and other causes. As with tolamolol, conversion to sinus rhythm has been an uncommon response to the drug, reflecting its negligible direct effect on the membrane potential of cardiac cells.[5,6,19] Practolol has also been reported to be of value in the treatment of ventricular arrhythmias after acute myocardial infarction.[2,7]

Clinical use in patients with pulmonary disease: The clinical importance of the cardioselectivity of tolamolol was demonstrated in our study. Six patients with substantial obstructive pulmonary disease received the drug with no untoward effects. Obstructive pulmonary disease has posed a major limitation on the use of propranolol because of its exacerbation of impaired respiratory function by inhibition of beta receptors of bronchial smooth muscle with resultant bronchoconstriction.[5,6,9–11] Tolamolol possesses a major advantage of applicability in this group of patients since, as a cardioselective $beta_1$ blocking agent, it has relatively little effect on $beta_2$ adrenoreceptors, which subserve bronchial smooth muscle.[5,6,12,13]

Comparison with propranolol: In addition to the beneficial aspects of tolamolol related to its cardioselectivity, clinical evaluation in our laboratories has demonstrated myocardial beta receptor inhibition quantitatively similar to that of propranolol with concomitantly less depression of cardiac function.[15] At doses of tolamolol and propranolol with equipotent attenuation of intrinsic cardiac chronotropic state, tolamolol was associated with less decrease in myocardial contractility, as indicated by indexes of contractile state. Further, the blockade of cardiac inotropic and chronotropic response to catecholomine infusion induced with tolamolol was quantitively similar to that induced with propranolol, and tolamolol had significantly less effect on systemic vascular resistance than propranolol.[15]

Untoward effects: The most significant untoward effect in our patients was hypotension, which occurred in three patients (16 percent). The reaction was transient but required vasopressor support in one patient. In a previous study, tolamolol produced a substantial reduction of blood pressure in three of four normotensive human volunteers.[12] These results indicate that intravenous administration of tolamolol requires careful observation of blood pressure and that the agent should not be utilized in states associated with hypotension or difficulty in maintenance of blood pressure.

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Patient-Initiated Rapid Atrial Pacing to Manage Supraventricular Tachycardia

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Patient-controlled rapid atrial pacing was used to manage 12 cases of recurrent supraventricular tachycardia refractory to drug therapy. The pacing system consists of an implanted receiver-lead system and an external patient-activated transmitter. In each case, brief periods (5 to 20 seconds) of rapid atrial pacing were effective in terminating the supraventricular tachycardia and resulted in a return to normal sinus rhythm. In three patients, occasional transient episodes of atrial flutter or atrial fibrillation preceded a spontaneous return to normal sinus rhythm. The pacing system was removed in one patient 13 months postoperatively because of persistent pericarditis; one patient died of an unrelated cerebral hemorrhage 13 months postoperatively. Successful management of supraventricular tachycardia has been maintained in the 10 remaining patients for 15 to 36 months (average 26.4). In more than 6,000 patient applications of rapid atrial pacing, there has been only one failure to convert the tachycardia.

Successful application of permanent rapid atrial pacing requires (1) prescreening of patients with temporary external rapid atrial pacing to verify susceptibility to conversion of supraventricular tachycardia and absence of anomalous conduction pathways that may permit conduction of rapid pacing rates to the ventricles, and (2) assessment of the patient's ability to use the transmitter properly.

Occasional transient episodes of supraventricular tachycardia are usually well tolerated by apparently healthy persons. However, these episodes may result in apprehension, emotional aberrancy, angina, syncope or congestive heart failure in persons with protracted recurrent episodes or in those with other underlying cardiovascular diseases.[1] Present techniques for control and management of supraventricular tachycardia in symptomatic patients can be grouped as follows:

1. *Drug therapy:* including administration of sedatives, digitalis, quinidine, procainamide, lidocaine and propranolol.
2. *Manual neural stimulation:* carotid sinus massage; other vagal stimulation such as the Valsalva maneuver.[2]
3. *Surgical intervention:* surgical interruption of atrioventricular conduction pathways.[3]
4. *Electrical stimulation:* direct current cardioversion; temporary rapid pacing[4]; artificial pacemakers[5,6]; carotid sinus nerve stimulation.[7]

This paper reports the results observed in 12 patients with recurrent episodes of supraventricular tachycardia refractory to multiple drug regimens who received an artificial pacemaker for self-management of these episodes.

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Materials and Methods

Pacemaker system and implantation: The pacemaker system used in this study consists of an implanted receiver-lead and a battery-powered externally worn patient-activated transmitter-antenna specially designed by Medtronic, Inc. Energy transmission between the transmitter and implanted receiver is accomplished through radiofrequency coupling. With the antenna connected to the transmitter and the transmitter activated by maintained depression of the on/off button on the transmitter, pulsed radiofrequency signals (carrier signal 480 kilohertz) are conducted to the windings of the antenna loop. When the antenna loop is placed in close proximity to the implanted receiver, pulsed radiofrequency energy radiating from the antenna is picked up by the receiver's internal antenna. Detecting and filtering circuits in the receiver transform the signal to nominal 2 msec stimulation pulses. Stimulator pulse frequency is controllable at the transmitter at rates of 50 to 300 pulses/min. The pulses are conducted by way of bipolar leads to the right atrium (Fig. 1). Pulse amplitude of the stimuli at the electrodes is dependent on the separation between the receiver and the antenna and is maximally 20 milliamperes when the separation is approximately 1 cm in air. The receiver is powered by the transmitted signal and therefore contains no power cells.

In each of 10 patients, a thoracotomy was performed and myocardial leads (Medtronic 5815) were sutured to the right atrial myocardium. The right atrial appendage was the attachment site of choice since the anterior and posterior walls of the appendage could be used to secure the electrode by passing sutures through the electrode foot plate and both appendage walls, thus providing more secure fixation to the relatively thin atrial myocardium.[8] This attachment also assures that the entire conducting coil of the electrode is in contact with myocardium. Alternate fixation sites such as the interatrial groove and right mid-atrium were utilized when surgical considerations dictated.

Two patients received endocardial atrial leads. Patient 5 had a J lead (American Optical Corp.) placed in the right atrial appendage. Patient 7 had a bipolar endocardial lead (Medtronic 5818) placed in the coronary sinus.

Patient selection: Participating patients were required to have documented poorly tolerated chronic recurrent supraventricular tachycardia unsuccessfully managed by more conservative techniques. In all, multiple drug regimens had been ineffective in preventing the onset or decreasing the duration of the tachycardia and carotid sinus massage and the Valsalva maneuver were also ineffective. Cardioversion was employed in several patients, but the recurrent nature of the tachycardia made this an ill tolerated procedure. Since the incidence of supraventricular tachycardia with accompanying morbidity was very low at any one center, the study was expanded to involve several centers, each using the same criteria for patient selection.

The effectiveness of rapid atrial stimulation in managing supraventricular tachycardia was established during the screening process.[9] Temporary pacing catheters were positioned in the right atrium, and conversion of supraventricular tachycardia was attempted using external pulse generators capable of asynchronous rapid pacing to rates of 300 pulses/min. Demonstration that pacing could terminate an episode of supraventricular tachycardia and concurrent verification that rapid pacing rates were not conducted to the ventricles by way of anomalous conduction pathways were required before permanent pacemaker implantation could be performed.

Surgical protocol: At surgery, stimulation thresholds necessary to pace the atria were taken after fixation of the leads using a temporary pacemaker. Thresholds below 3 milliamperes were considered adequate for stimulation with the pacemaker system. After the implantable receiver was connected to the leads, a sterile antenna was placed over the receiver and atrial pacing was instituted using the entire system to verify proper operation. This procedure was repeated after the receiver was totally implanted to reverify correct operation of the system.

Patient-initiated pacing: Most patients receiving the pacemaker experienced episodes of supraventricular tachycardia during the post-surgical hospitalization. These episodes were successfully managed using the pacemaker system (Fig. 2).

Before discharge, each patient was instructed in correct use of the transmitter. During an episode of supraventricular tachycardia, he was to adjust the pacing rate to the rate that had effectively converted the tachycardia during the screening and evaluation process and then to activate the transmitter by depressing the on/off button for five to twenty seconds. If relief was not obtained after the first application, a second attempt was to be made. Failure of the tachycardia to revert after two successive applications was to be reported immediately.

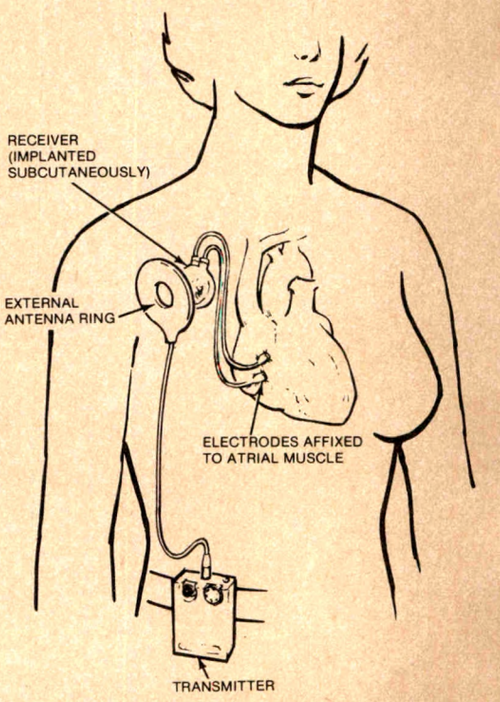

FIGURE 1. Schematic representation of the radiofrequency pacemaker system implanted and ready for patient activation.

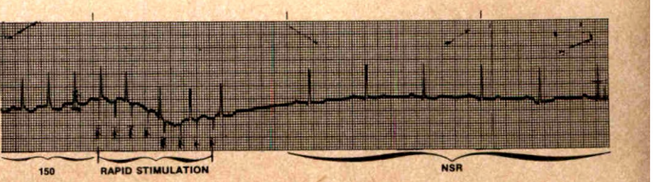

FIGURE 2. Return to normal sinus rhythm (NSR) after a brief application of rapid atrial stimulation at 250 pulses/min using the radiofrequency pacemaker.

Results

Patient-initiated rapid atrial stimulation with the described pacing system has been used successfully in more than 6,000 applications (based on extrapolation of frequency of use and months of follow-up) by the 12 studied patients. Table I summarizes the observed results. Frequency of application ranged from 10/day to approximately 1/month. In one patient (Case 6) attempts at conversion failed to terminate the arrhythmia on a single occasion. When she reported for treatment, pacing with the pacemaker at several different rates (150, 180, 200, 300 pulses/min) failed to convert the tachycardia. However, starting pacing at 120 pulses/min and slowly increasing the pacing rate to 200 and then switching the transmitter to the off position resulted in a return to sinus rhythm. This patient has since had no episode of supraventricular tachycardia refractory to rapid atrial stimulation.

In one patient (Case 1) the pacing system was removed 13 months postoperatively because of persistent pericarditis. One patient (Case 10) died 3 months postoperatively after an unrelated massive cerebral hemorrhage confirmed at autopsy. In the 3 months after implantation, this patient used the system successfully on four occasions. Effective management of supraventricular tachycardia has been maintained in the 10 remaining patients in the study for 15 to 36 months (average 26.4).

The usual result of brief rapid stimulation of the atria during an episode of tachycardia was a return to sinus rhythm. Two patients occasionally experienced atrial fibrillation with a resulting ventricular rate of 60 to 70 beats/min. These fibrillatory episodes spontaneously reverted to sinus rhythm within minutes or hours. Two patients occasionally had brief periods of atrial flutter that spontaneously reverted to sinus rhythm.

Illustrative Cases

The following case studies are presented as typical.

Case 11

A 66 year old man was admitted to the hospital in May 1972 with persistent palpitations. He had a 7 year history of episodes of similar palpitations. There was no history of rheumatic fever, hypertension, diabetes mellitus, dizziness, syncope or manifestations of congestive heart failure. During this hospitalization, numerous episodes of paroxysmal atrial tachycardia (heart rate 166 beats/min) were recorded. These episodes were converted to sinus rhythm with carotid sinus massage. During the next 15 months, the patient was readmitted to the hospital 10 times with episodes of more than 1 hour's duration of paroxysmal atrial tachycardia that did not revert spontaneously with the Valsalva maneuver or carotid sinus massage. During these hospital admissions, carotid sinus massage followed by administration of edrophonium, phenylephrine, diazepam, propranolol, diphenylhydantoin and occasionally lidocaine was successful in converting the paroxysmal atrial tachycardia. This patient was receiving maintenance doses of digoxin and quinidine; after an allergic reaction to quinidine, he was given procainamide instead. At least 100 episodes of paroxysmal atrial tachycardia had been documented during these periods of hospitalization. Because of the frequency and long duration of the episodes and the inability of normal medication regimens to suppress the episodes, a radiofrequency-coupled pacemaker was implanted in August 1973. Each subsequent episode of paroxysmal atrial tachycardia has been successfully converted to sinus rhythm with rapid atrial pacing, initially at 240 pulses/min and now at 200 pulses/min. The patient is being maintained on a regimen of digoxin, procainamide and propranolol. The frequency of paroxysmal tachycardia has decreased since implantation to about 1 episode/month. The cause of this decrease is unclear.

Case 8

A 58 year old man, has had since age 14 episodes of palpitations that reverted spontaneously to sinus rhythm. Wolff-

TABLE I

Summary of 12 Cases of Radiofrequency Pacemaker Implantation

Patient	Date of Implantation	Age at Implantation (yr)	Effect of Rapid Atrial Pacing	Frequency of Attack	PPM	Concurrent Drug Therapy
1	7/70*	22	NSR, AVB (100/min), AFI	10/day	—	—
2	2/72	46	NSR	10–15/week	280	Digoxin, quinidine, diazepam
3	2/72	42	NSR	3/week	300	Propranolol
4	4/72	23	NSR	2–4/day	300	—
5	5/72	44	NSR, AF (60/min), AFI [4:1]	2–3/week	300	Digoxin
6	2/73	61	NSR†	3–4/week	150–200	Propranolol
7	3/73	55	NSR	1/month	300	Procainamide
8	3/73	58	NSR	3/month	300	Digoxin
9	4/73	45	NSR	7–10/week	200	—
10‡	6/73	—	NSR or AF (70/min)	1/month	250–300	—
11	8/73	67	NSR	2/month	200	Procainamide, propranolol, digoxin
12	11/73	52	NSR	1–2/week	300	Digoxin

* Unit removed in August 1971 because of refractory episodes of pericarditis.
† One refractory episode occurred (see text).
‡ Patient died in September 1973. Autopsy revealed massive cerebral hemorrhage.
Figures in parentheses indicate resulting ventricular rate.
AF = atrial fibrillation; AFI = atrial flutter; AVB = atrioventricular block; NSR = normal sinus rhythm; PPM = most effective pacing rate (pulses/min).

Parkinson-White syndrome (type B) and paroxysmal atrial tachycardia were diagnosed. He has been admitted to the hospital six times since October 1971 with episodes of paroxysmal atrial tachycardia lasting for hours (usually converted with intravenously administered metaraminol) and has frequently been treated in the emergency room. With the increased frequency of paroxysms, the patient's life style changed considerably; he lived in fear of the attacks, became incapacitated and was not able to work. Before pacemaker implantation, the tachycardia was not controlled with administration of digoxin, propranolol, sodium diphenylhydantoin, quinidine or diazepam, singly or in various combinations. In March 1973, a receiver and two pediatric leads, placed on the upper right atrium, were implanted. The patient now converts his episodes of tachycardia (0 to 3/month) using a setting of 300 pulses/min. The drug regimen is 0.25 mg of digoxin daily. After recovery from the implantation, the patient returned to work and resumed normal daily activities.

Discussion

The patients selected for study all had a history of recurrent attacks of supraventricular tachycardia that were not well managed with drug therapy and required frequent use of other techniques such as manual vagal stimulation or direct current cardioversion. These techniques must be applied under constant physician control, are not universally or consistently effective and are of some risk to the patient.[10] Carotid sinus massage, for instance, carries with it the risk of cardiac standstill if an exaggerated vagal response occurs. It may also result in cerebral strokes possibly as a result of release of a carotid plaque during massage and it is therefore contraindicated in the aged or patients with cerebral vascular disease.[2] In patients with frequent ill tolerated episodes of supraventricular tachycardia, the dependence on outside intervention often becomes debilitating in itself.

Modes of conversion to sinus rhythm with rapid atrial pacing: The return to sinus rhythm after application of rapid atrial stimulation may involve several mechanisms: (1) Rapid atrial stimulation may produce atrial fibrillation or flutter, which are unstable rhythms and therefore tend spontaneously to revert to normal sinus rhythm. (2) Application of asynchronous rapid stimuli may interrupt a reentry pathway by depolarizing atrial portions of the pathway necessary to maintain rapid rhythms. (3) When an ectopic atrial focus is responsible for the tachycardia, application of rapid stimuli to the atria may result in overdrive suppression of the ectopic focus. This study was not designed to determine the specific mechanism responsible for conversion in any specific case.

Potential risks of method: Several potential complications related to rapid atrial stimulation have been reported and should be considered when applying this management technique. They include: (1) Ventricular stimulation and possible ventricular tachycardia or fibrillation. This may result from poor lead placement or may be due to the existence of anomalous conduction pathways bypassing normal atrioventricular conduction (as in the Wolff-Parkinson-White syndrome).[4,11] (2) Asystole following pacing. (3) Patient discomfort due to pacing impulses.[10,12] These complications could also be expected to occur with the radiofrequency-coupled system, but we believe that they can be minimized by careful screening using temporary pacing, and by observing the first several episodes after pacemaker implantation.[13] In this study, atrial epicardial leads were applied to minimize the chances of ventricular stimulation in 10 patients. Endocardial leads were used in two patients, and it would be reasonable to assume that with use of these leads there is an added risk for potential inadvertent ventricular stimulation through dislodgment of the leads, and more frequent evaluation would be required. As a precaution against catastrophic ventricular stimulation resulting from transvenous endocardial lead dislodgement and migration, we recommend a protocol requiring physician-monitored application of rapid stimulation for each episode of tachycardia during the first several months after endocardial lead implantation.

Requirements for patient selection: Since this pacemaker is patient-activated and controlled, careful assessment of the patient's ability to use the device must be made. A feeling by the attending physician that the patient would not properly use the transmitter was a reason for rejecting that patient for this treatment. The patient must be able to (1) recognize that a rhythm disturbance is occurring, (2) initiate stimulation at the physician-prescribed pulse frequency, (3) maintain stimulation for up to 20 seconds, and (4) recognize whether the tachycardia has been successfully converted. One patient in the group studied was not able to perceive correctly and distinguish between a real and imagined attack and therefore tended grossly to overuse the transmitter. Also, it is evident that, since the use of myocardial leads is strongly recommended, the patient's physical condition should be adequate to tolerate the thoracotomy required for their implantation.

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Permanent Pacing in Patients With Transient Trifascicular Block During Acute Myocardial Infarction

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Patients with acute myocardial infarction and transient complete atrioventricular (A-V) block in association with right bundle branch block and left anterior hemiblock have a high incidence rate of late sudden death presumably due to recurrent A-V block. Over a 5 year period, 18 patients demonstrated right bundle branch block and left anterior hemiblock and had transient complete block during an acute myocardial infarction and survived to hospital discharge. Of six patients who did not have permanent pacing, five died suddenly (one was lost to follow-up) with a mean survival time of 2.4 months after hospital discharge. Twelve subsequent patients received permanent demand pacemakers and had a significantly improved prognosis with a mean survival time of 18 months ($P < 0.001$). Six patients were still alive at an average follow-up time of 20 months. Prophylactic permanent pacing significantly improves the prognosis after acute myocardial infarction in this select subgroup of patients.

Acute coronary care with continuous electrocardiographic monitoring has significantly reduced the in-hospital mortality of patients suffering from acute myocardial infarction. However, late sudden death continues to be a major problem in patients surviving an acute infarction.[1] It is essential to identify and to treat aggressively any subgroup of patients who have an increased risk of sudden death after infarction. Recently patients who demonstrate ventricular irritability after infarction have been given attention in the expectation that appropriate antiarrhythmic treatment may reduce the incidence of sudden death due to arrhythmias.[2] Likewise, patients who experience transient complete atrioventricular (A-V) block in association with right bundle branch block and left anterior hemiblock at the time of infarction also have a high incidence rate of late sudden death, presumably due to a recurrence of the complete A-V block.[3,4] Death due to advanced A-V block may be prevented by implantation of a permanent demand pacemaker.

Our group recently reviewed a series of 425 patients with acute myocardial infarction that included 6 patients with transient complete A-V block and right bundle branch block plus left anterior hemiblock. Five of these patients died suddenly within 6 months after hospital discharge and one was lost to follow-up.[5] In view of this high mortality rate we instituted a policy of prophylactically inserting permanent demand pacemakers in this group of patients. This report (1) presents the follow-up data of the 12 patients given permanent pacing because of transient complete A-V block with right bundle branch block and left anterior hemiblock during their initial hospitalization for acute myocardial infarction and (2) compares survival data for patients with and without such treatment.

Methods

The medical records were reviewed of 1,061 patients admitted to the coronary care unit at Parkland Memorial Hospital over a 60 month period with the diagnosis of acute myocardial infarction. Of 71 patients (7 percent) identified who

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had right bundle branch block and left anterior hemiblock during their clinical course, 33 (46 percent) had transient complete A-V block during acute infarction. Of these 33 patients, 15 (47 percent) died after pump failure before hospital discharge; 6 were discharged without permanent pacing (including 1 lost to follow-up); and 12 consecutive subsequent patients were discharged with prophylactic permanent demand pacemakers. Except for the presence of permanent pacemakers there was no difference between surviving patients with and without pacing therapy.

The diagnosis of acute myocardial infarction was established by a history of chest pain in association with typical enzyme changes or characteristic electrocardiographic changes, or both. The criteria for right bundle branch block were those of Bauer[6] and Scanlon[7] and their associates and the criteria for hemiblock were those of Rosenbaum et al.[8]

Results

Clinical course of patients with permanent pacing: In all 12 patients complete A-V block occurred after the development of right bundle branch block and left anterior hemiblock. Temporary transvenous demand pacemakers were inserted without complications at the time the ventricular conduction defect was noted. Complete A-V block was transient with the reestablishment of sinus rhythm and a normal P-R interval in all patients except one who had atrial fibrillation with normal A-V conduction.

Right bundle branch block with left anterior hemiblock was evident in the admission electrocardiogram of nine patients; in eight patients these changes were not evident in previous electrocardiograms; one patient had no prior electrocardiogram. In the remaining three patients these electrocardiographic changes developed during the stay in the coronary care unit.

After the patient's condition had stabilized, premature ventricular beats were no more frequent than 1/min in any case. A permanent Starr-Edwards or Medtronic demand pacemaker was implanted 1 to 3 weeks after infarction. All patients were subsequently followed up in a pacemaker clinic. At no time did their symptoms or electrocardiographic changes suggest pacemaker failure. Seven patients were in New York Heart Association functional class III and five were in class II at the time of pacemaker implantation.

Survival data: Individual clinical data are listed in Table I. The mean age at the time of infarction was 68 years. In 8 of the 12 patients the infarction was anterior,

TABLE I

Patients Receiving Permanent Demand Pacemakers

Case no.	Age (yr) & Sex	Location of Infarct	Follow-Up Period (mo)	Results	NYHA Class
1	78M	Anterior	42	Alive; CHF	III
2	66M	Anterior	36	Alive; angina	II
3	61M	Anterior	16	Alive; doing well	III
4	67M	Anterior	12	Alive; CHF	III
5	80F	Inferior	10	Alive; doing well	II
6	60M	Anterior	5	Alive; doing well	II
7	68F	?	25	Died; CHF	III
8	78M	?	23	Died; CHF	III
9	68M	Anterior	23	Sudden death	II
10	62M	Anterior	15	Died; CHF; recurrent MI	III
11	58M	Inferior	12	Sudden death	II
12	78M	Anterior-lateral	2	Died; pneumonia	III

CHF = congestive heart failure; MI = myocardial infarction; NYHA Class = New York Heart Association functional class.

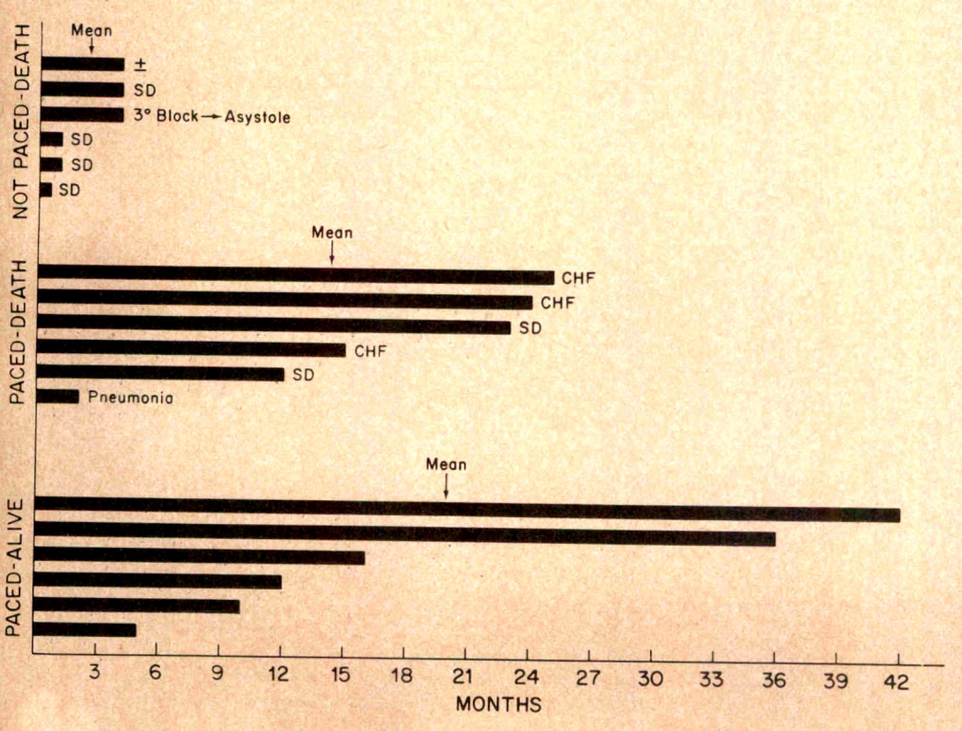

FIGURE 1. Individual follow-up data of patients with transient complete atrioventricular block associated with right bundle branch block and left anterior hemiblock developing during an acute myocardial infarction. Two groups were treated with permanent pacing and one was not. CHF = congestive heart failure; SD = sudden death; ± = patient lost to follow-up at 4 months. **Arrows** indicate mean survival time for each group.

in 2 it was inferior and in 2 a precise location could not be established because of extensive ventricular conduction disturbances. The mean survival time for the total patient group was 18 months. Six patients were alive at the end of the follow-up period (mean 20 months) and six had died (mean 15 months). The cause of death was congestive heart failure in three patients (mean survival time 18 months) and bronchopneumonia in one patient (survival time 2 months). Two patients died suddenly of unknown cause 12 and 23 months, respectively, after pacemaker insertion. Neither patient had a documented arrhythmia or pacemaker failure before death.

Figure 1 presents follow-up data in the patients treated with and without pacing. The six patients who did not undergo pacing have been described previously.[5] All six had conduction disturbances identical to those of the patients who underwent pacing, and there were no significant differences in age, sex, location of acute myocardial infarction or clinical state between the two groups of patients. Patients in both groups received similar therapy except for permanent pacing. The mean survival time of the patients without pacing was 2.4 months. Four of the five patients died suddenly at home, and one was unconscious on arrival at the emergency room where advanced A-V block leading to asystole was diagnosed before death. In two patients autopsy examination revealed no acute cause for sudden death (including no recurrent acute myocardial infarction), thus suggesting that death was due to advanced A-V block or arrhythmia. One patient was lost to follow-up at 4 months.

There was a striking difference in survival time between the patient groups treated with and without pacing (Fig. 1). The survival time of patients treated without pacing was 2.4 months compared with the mean of 18 months for all 12 patients treated with pacing ($P < 0.001$) or the mean of 15 months ($P < 0.01$) for the six patients treated with pacing who had died at the time of follow-up (Fig. 1, paced-death group). All of the patients treated without pacing died suddenly, whereas three of the six treated with pacing died of congestive heart failure, one died of pneumonia, and only two died suddenly. The mean survival time to date for patients treated with pacing who are currently alive is 20 months.

Discussion

The management of patients who have transient complete A-V block in association with right bundle branch block and left anterior hemiblock has remained controversial. Several studies have revealed a high incidence rate of late sudden death in patients with such changes in association with acute myocardial infarction. Scanlon et al.[7] found that five of eight such patients died suddenly within 8 months of initial hospital discharge. Godman et al.[9] and Pryor[10] also reported an increased risk of late sudden death in this patient group. Waugh et al.[4] observed that six of eight such patients untreated with pacing died suddenly within a 12 month follow-up period. Because of this high mortality rate they treated seven similar patients with pacing and found no instances of sudden death in 12 months. In contrast, Waters et al.[11] observed no sudden death in a small group of two patients treated without pacing and one patient treated with pacing with a short follow-up time.

Godman et al.[9] have suggested that most patients with extensive conduction abnormalities at the time of acute myocardial infarction have severe underlying coronary artery disease with extensive myocardial necrosis. Aggressive treatment with pacing does not improve survival in this group of patients since the poor prognosis is due to loss of myocardial function.[9]

Our series strongly suggests that permanent demand pacing improves the long-term prognosis. Patients treated with pacing had on average a 16 month longer survival time than patients with similar clinical characteristics who were not so treated. The contention that these patients have severe coronary disease is supported by the high overall mortality rate due to pump failure (CHF, Fig. 1) even with pacing.

Insertion of temporary and subsequently permanent demand pacemakers was not associated with any significant complications. Most of the patients treated with pacing were able to lead relatively normal lives.

Clinical implications: The total number of patients with the syndrome of transient complete A-V block, right bundle branch block and left anterior hemiblock during acute myocardial infarction is small. However, in light of the alarming rate of sudden death in patients not treated with pacing that we and others[4,7,9–11] have observed, further randomized studies of pacing therapy on this group seem unjustified. Patients with transient A-V block in association with right bundle branch block and left anterior hemiblock during acute myocardial infarction should be given permanent pacing to prevent late sudden death.

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Addendum

Since this manuscript was prepared, Patient 1 has died of congestive heart failure, 46 months after implantation. Patients 2 through 6 are still alive and in the condition described in Table I. An additional patient has undergone implantation and is alive, in New York Heart Association functional class II, 13 months after the procedure.

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Comparative Response of Right and Left Ventricles To Volume Overload

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The cardiac volume data of 49 normal children were compared with those of 23 with secundum atrial septal defect and 24 with patent ductus arteriosus. Significantly smaller ventricular end-diastolic volumes were observed in the normal infants than in older children (right ventricle 53.9 versus 75.5 cm^3/m^2; left ventricle 46.7 versus 63.6 cm^3/m^2). "Distensibility" of the right ventricle (D_{RV}), left ventricle (D_{LV}) and left atrium increased normally with age. D_{RV} and D_{LV} were similar shortly after birth; thereafter, D_{RV} increased more rapidly than D_{LV} (mean D_{RV} 12.7; mean D_{LV} 7.8 cm^3/m^2 per mm Hg, $P < 0.001$). In both atrial septal defect and patent ductus arteriosus, the ipsilateral (involved) ventricles had increased volume, increased output, normal ejection fraction and increased distensibility. The contralateral (left) ventricle in atrial septal defect was smaller than normal (39.6 versus 49.7 cm^3, $P < 0.001$), and had a smaller ejection fraction (0.63 versus 0.71, $P < 0.01$) and output (3.70 versus 4.57 liters/min per m^2, $P < 0.005$). In contrast, the contralateral (right) ventricle in patent ductus arteriosus remained normal. Left atrial maximal volume was larger than normal in atrial septal defect (46.6 versus 35.9 cm^3/m^2, $P < 0.001$). The left atrial and left ventricular volumes in patent ductus arteriosus were, respectively, 152 and 142 percent of normal, indicating comparable response to the volume load. The left heart changes in atrial septal defect may be related both to a functionally restrictive defect and to the difference in distensibility of the ventricles.

Angiocardiography provides anatomic details of the heart and great vessels not reproducible by any other method. The excellent radiologic reproduction has enabled estimation of left ventricular,[1–5] right ventricular,[5–8] left atrial[4,9–11] and right atrial[12] volumes as additional measures of cardiac performance. This approach is especially useful for the comparative analysis of right and left heart function.

The purpose of this investigation was to evaluate the response of the ipsilateral (involved) ventricle and of the contralateral (unaffected) ventricle to isolated volume overload of the right or left heart. The pressure and volume data of the right ventricle, left ventricle and left atrium of 23 children with isolated secundum atrial septal defect and of 24 children with isolated patent ductus were analyzed. These values were compared with similar data obtained from 49 children with normal hemodynamic status.

Materials and Methods

Volume estimation: The methods used to estimate the volume of the ventricles and left atrium have been reported previously.[5,9] The surface areas of the frontal and lateral images were obtained from the angiocardiograms by planimetry; in addition, the distances from apex to base in the ventricular images and the maximal diameters in the left atrial images were measured. Volume calculation was by the parallelepiped method for the ventricles[5,13] and by the area-length method for the left atrium.[9] The initial volume estimates were corrected by regression equations specific for each chamber: $V_c = 0.65\ V_e + 0.01$ (right

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TABLE I

Cardiac Chamber Volumes Related to Body Surface Area in Normal Children

	r	Regression Equation
RVEDV		
Infants (no. = 10)	0.75	$V(cm^3) = 60.29\ BSA - 2.69$
Children (no. = 34)	0.94	$V(cm^3) = 93.53\ BSA - 15.25$
LVEDV		
Infants (no. = 10)	0.84	$V(cm^3) = 73.65\ BSA - 8.85$
Children (no. = 39)	0.89	$V(cm^3) = 63.77\ BSA - 0.16$
LA_{max}		
Infants (no. = 10)	0.84	$V(cm^3) = 47.40\ BSA - 4.63$
Children (no. = 37)	0.87	$V(cm^3) = 37.58\ BSA - 0.90$

BSA = body surface area (in m^2); LA_{max} = left atrial maximal volume; LVEDV = left ventricular end-diastolic volume; *r* = correlation coefficient; RVEDV = right ventricular end-diastolic volume; V = volume.

TABLE II

Comparative Values for Chamber Volume and Ventricular Output in Normal Infants and Children (mean ± standard error)

Variable	Children (2 to 19 yr)	Infants (4 days to 14 mo)	*P* Value
Heart rate (beats/min)	106.21 ± 2.57 (no. = 39)	135.5 ± 5.4 (no. = 10)	<0.001
RVEDV (cm^3/m^2)	75.48 ± 2.26 (no. = 34)	53.86 ± 3.14 (no. = 10)	<0.001
RVO (liter/min per m^2)	4.83 ± 0.25 (no. = 34)	4.2 ± 0.24 (no. = 10)	NS
LVEDV (cm^3/m^2)	63.56 ± 1.83 (no. = 39)	46.67 ± 3.28 (no. = 10)	<0.001
LVO (liter/min per m^2)	4.77 ± 0.19 (no. = 37)	4.22 ± 0.22 (no. = 9)	NS
LA_{max} (cm^3/m^2)	36.63 ± 1.13 (no. = 34)	33.82 ± 2.37 (no. = 10)	NS

LA_{max} = left atrial maximal volume; LVEDV = left ventricular end-diastolic volume; LVO = left ventricular output (systemic blood flow); NS = not significant; *P* value = level of significance (*t* test); RVEDV = right ventricular end-diastolic volume; RVO = right ventricular output (pulmonary blood flow).

ventricle); $V_c = 0.77\ V_e + 1.17$ (left ventricle); and $V_c = 1.143\ V_e + 0.14$ (left atrium) where V_c = corrected volume and V_e = initial estimate. These equations have been derived from in vitro studies relating true volumes of casts made of the heart to the volumes estimated from the radiologic images.[9,13]

The angiocardiograms were obtained in the frontal and lateral projections using Phillips biplane, dual mode (5 and 9 inch [12.7 and 22.9 cm]) cesium iodide image intensifier tubes with fixed tube to film distances of 81 cm in the frontal projection and 89 cm in the lateral projection. A Datacor system facilitated timing of each X-ray exposure through display of the electrocardiogram and pressure-pulse curve in the cine film. The electrocardiogram and pressure curves were also recorded on paper at speeds of 50 or 75 mm/sec. Different correction factors for X-ray magnification were used for the three chambers depending on their respective distances from the X-ray grids.[14]

Protocol: The infants were studied without sedation; the older children were given Demerol® and Vistaril® intramuscularly (1.5 to 1.8 mg/kg body weight of each, up to 50 mg) for premedication. For the Fick cardiac output calculations, oxygen consumption was determined only in 10 children in the normal group, in 5 of those with atrial septal defect and in none of those with patent ductus arteriosus; in the rest, normal oxygen consumption[15] was assumed. Cineangiocardiography was performed after cardiac catheterization; 35 mm movie cameras were used at filming rates of 80 frames/sec in the infants and 64 frames/sec in the older children. Renografin 76® in a dose of 1.0 to 1.5 ml/kg was used as the contrast medium. For the right ventricular analysis, the contrast material was injected into the right atrium to avoid ventricular arrhythmias that otherwise frequently occur during high pressure injection into the ventricles. A second injection of contrast medium was usually made into the pulmonary trunk for diagnostic purposes or better visualization of the left ventricle, or both. At least 10 minutes was allowed between injections. In 15 children with atrial septal defect and in 21 with patent ductus arteriosus, the right atrial angiocardiograms were of sufficient contrast to enable border delineation of the left atrium and left ventricle as well. In the remaining patients, the left heart volume analyses were derived from the pulmonary angiograms. The heart rates at the time of right and left heart opacification were essentially identical during the atrial angiograms; the heart rates during the pulmonary angiograms did not differ by more than 10 beats/min from those during the corresponding atrial angiograms.

Case material: The 23 infants and children with atrial septal defect ranged in age from 0.3 to 14.6 years (mean 5.4), and the 24 with patent ductus arteriosus from 2 weeks to 9 years (mean 3.4 years). The diagnosis was surgically confirmed in all but seven of the former and two of the latter who are still awaiting surgery. The left to right shunt was localized by hydrogen inhalation curves, blood oxygen analyses and selective angiocardiography. No patient had congestive heart failure or a right to left shunt. There was no associated valvular stenosis or regurgitation. Postoperative clinical evaluation revealed normal cardiac findings.

The cardiac chamber volumes of 49 children with normal cardiac catheterization findings were also analyzed. These children were referred for hemodynamic evaluation because of suspected organic heart disease or unusual chest roentgenographic findings (vascular ring, mediastinal or pulmonary mass, pericardial cyst, for example) requiring supplementary angiographic studies. Patients with demonstrable cardiac abnormality, even though mild, and those with previous cardiac surgery were excluded from this group. The angiocardiograms were obtained similarly, with injection of contrast medium into the right atrium. Border delineation of the left heart chambers was made from these angiograms. These normal data represent an expansion of our previous study.[14]

Determinations: Technically poor cineangiocardiograms showing poor contrast, subject motion or arrhythmia were not analyzed. The end-diastolic volume, end-systolic volume, stroke volume and ejection fraction of the right and left ventricles and left atrial maximal volume were determined. Right and left ventricular output measurements were obtained by multiplying the respective stroke volume by heart rate. Ejection fraction was represented by the ratio between stroke volume and end-diastolic volume. In both atrial septal defect and patent ductus arteriosus, the difference between the right and left ventricular output values represented shunt flow per

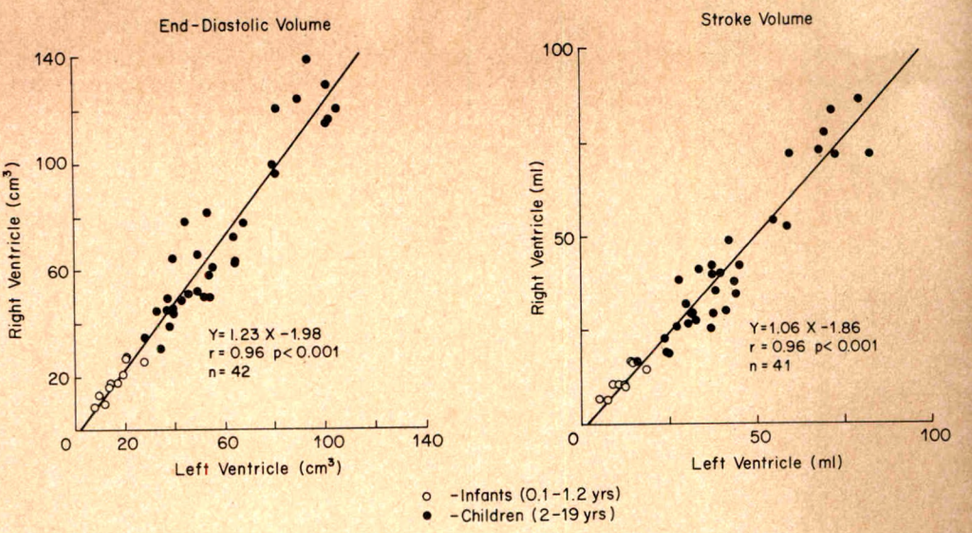

FIGURE 1. Comparison of right and left ventricular end-diastolic and stroke volumes in normal children. Regression lines have been drawn.

minute. The ratio between ventricular end-diastolic volume and end-diastolic pressure was also used as a rough index of "ventricular distensibility." The ratio of left atrial maximal volume to the corresponding peak V wave pressure, obtained from pulmonary capillary wedge or direct left atrial recordings, was likewise used to represent "atrial distensibility." More elaborate indexes of chamber distensibility such as Δvolume/Δpressure were not derived since the pressures were obtained by a liquid-filled catheter-transducer system with limited frequency response.

Results

Normal Data

The patients were 10 infants aged 4 days to 14 months and 39 children aged 2.3 to 19.4 years (mean 8.2). Good correlation between right ventricular end-diastolic volume, left ventricular end-diastolic volume or left atrial maximal volume and body surface area was observed. The respective correlation coefficients (r) and regression equations are shown in Table I. When corrected for body surface area, the ventricular volumes in the infant group were smaller than those in the older children (Table II). The stroke index in the former (31.9 ± 2.11 cm^3/m^2 [mean ± standard error]) was also smaller than that in the latter (45.2 ± 1.43, $P < 0.001$). However, because of the difference in heart rates, cardiac index did not differ significantly in the two groups although it was smaller in the infants.

The end-diastolic volume of the right ventricle (RVEDV) was generally larger than that of the corresponding left ventricle (LVEDV). This was observed in both the infants and older children; this relation is expressed by the regression equation RVEDV = 1.23 LVEDV − 1.98. However, the stroke output values of both ventricles were practically identical (Fig. 1). The angiographically derived ventricular output (stroke output times heart rate) correlated well with cardiac output assessed with the Fick method (Table III). Because the right ventricle had a larger volume, its ejection fraction (0.59 ± 0.01) was lower than that of the left ventricle (0.71 ± 0.01, $P < 0.001$).

TABLE III

Comparison of Angiographically and Fick-Derived Pulmonary and Systemic Blood Flow Values

	Normal		ASD		PDA	
	Angio	Fick	Angio	Fick	Angio	Fick
PBF	4.65	4.85	7.19	8.82	6.63	8.49
	(no. = 42)		(no. = 21)		(no. = 23)	
	$r = 0.86$		$r = 0.79$		$r = 0.77$	
	$P < 0.001$		$P < 0.001$		$P < 0.001$	
SBF	4.72	4.90	3.70	4.14	4.17	4.18
	(no. = 44)		(no. = 19)		(no. = 21)	
	$r = 0.83$		$r = 0.83$		$r = 0.88$	
	$P < 0.001$		$P < 0.001$		$P < 0.001$	

Angio = angiographically derived value; ASD = atrial septal defect; Fick = value derived with the Fick method; P = level of significance; PBF = pulmonary blood flow (liters/min per m^2); PDA = patent ductus arteriosus; r = correlation coefficient; SBF = systemic blood flow (liters/min per m^2).

Effect of age: Figure 2 shows the right and left ventricular end-diastolic volume/pressure ratios plotted against age. Increasing distensibility with age was more evident in the right than in the left ventricle as shown by the respective regression lines. The initial segments of these lines were comparable shortly after birth; however, that of the right ventricle rose rapidly during the first year (Fig. 2, left) followed by a less steep slope thereafter (Fig. 2, right). The left ventricular regression line assumed a nearly uniform and less rapid increase with age. Mean distensibility index of the right ventricle was 12.7 ± 0.08 cm^3/m^2 per mm Hg whereas that of the left ventricle was 7.8 ± 0.47 ($P < 0.001$). Distensibility of the left atrium also tended to increase with age (Fig. 3). For all three chambers, this increase in distensibility appeared to be related chiefly to increase in volume since no significant change in the corresponding filling pressures was observed.

As in our previous studies,[9,14] a positive correlation was observed between the maximal volumes of all three chambers and age, height and weight, but correlation

with heart rate was negative. The regression formulas for predicting the normal maximal volumes of the right ventricle, left ventricle and left atrium, based on the present data, are shown in Table IV.

Right Ventricular Volume Overload (Atrial Septal Defect)

The changes in the end-diastolic volume of the ipsilateral right ventricle and contralateral left ventricle are shown in Figure 4, in which the observed and corresponding predicted normal values are plotted against body surface area. As shown by the regression lines, significant right ventricular enlargement was present (mean 91.4 ± 10.8 versus 54.9 ± 6.0 cm^3, $P < 0.001$). In contrast, small left ventricular size was observed (mean 39.6 ± 4.5 versus 49.7 ± 5.2 cm^3, $P < 0.001$). When normalized for body surface area, the mean end-diastolic volume of the right ventricle was 120.6 ± 5.6 cm^3/m^2, whereas that of the left ventricle was 52.6 ± 2.75 cm^3/m^2. The mean ejection fraction of the right ventricle was 0.58 ± 0.01 and that of the left ventricle 0.63 ± 0.01. The latter was lower than the normal value ($P < 0.01$). Mean right ventricular output was 7.19 ± 0.44 liters/min per m^2, and mean left ventricular output 3.7 ± 0.24. The latter was smaller than the predicted normal value of 4.57 liters/min per m^2 ($P < 0.005$).

Comparison of values for angiographically derived pulmonary flow (right ventricular output [Q_{RV}]) and angiographically derived systemic flow (left ventricular output [Q_{LV}]) with the corresponding values obtained

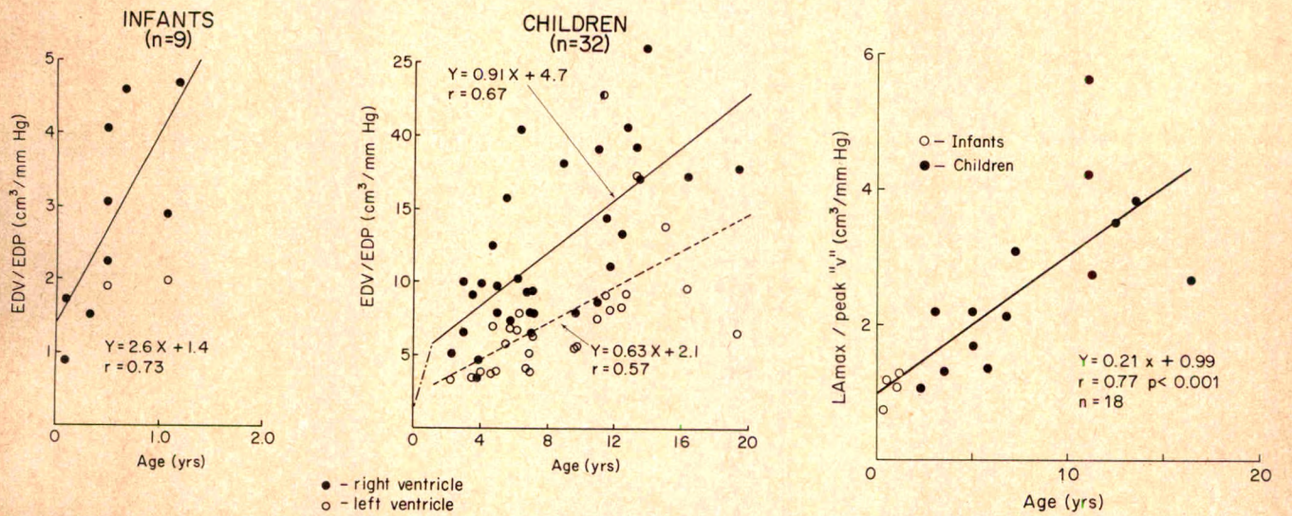

FIGURE 2 (left and center). Ventricular "distensibility" in normal infants and children, plotted against age. **Solid line** is the regression line for the right ventricle, and the **dashed line** that for the left ventricle. The infant group **(left panel)** has a steep right ventricular regression slope also represented by the **long-short dashed line (right panel).** Note the dual slopes of the right ventricular regression line not observed in the left ventricular regression. EDV/EDP = ratio between end-diastolic volume and pressure.

FIGURE 3 (right). Left atrial "distensibility" in normal infants and children, plotted against age. Increasing left atrial distensibility with age is shown by the regression line. LAmax = left atrial maximal volume.

TABLE IV
Multiple Regression Equations for Predicting Normal Chamber Volumes In Children*

Chamber (cm^3)	Regression Equation	r^2	95% Confidence Limits (± 2 SD) † (%)
	A. Infants		
RVEDV	V = 12.46 (age) − 0.029 (ht) + 1.74 (wt) + 0.070 (HR) − 7.65	0.96	86 − 114
LVEDV	= 10.61 (age) − 0.336 (ht) + 1.77 (wt) − 0.046 (HR) + 26.43	0.88	71−129
LA_{max}	= 3.09 (age) − 0.117 (ht) + 0.93 (wt) − 0.103 (HR) + 24.89	0.92	64 − 136
	B. Children		
RVEDV	V = 2.03 (age) + 0.291 (ht) + 1.19 (wt) + 0.009 (HR) − 11.44	0.90	68 − 132
LVEDV	= 4.22 (age) − 0.329 (ht) + 1.00 (wt) − 0.178 (HR) + 62.03	0.84	67 − 133
LA_{max}	= 2.74 (age) − 0.268 (ht) + 0.57 (wt) − 0.034 (HR) + 34.73	0.83	65 − 135

*Data based on 10 infants and 39 children; using age in years, height (ht) in centimeters, weight (wt) in kilograms, and heart rate (HR) in beats per minute.

†95% confidence limits = ± 2 standard deviations (SD) for range of observed/predicted X 100 (%).

LA_{max} = left atrial maximal volume; LVEDV = left ventricular end-diastolic volume; r^2 = multiple correlation coefficient; RVEDV = right ventricular end-diastolic volume; V = volume.

by the Fick method (Q_p and Q_s, respectively) revealed good correlation (Table IV). The mean Q_{RV}/Q_{LV} ratio was 2.09 ± 0.14, and the Fick derived Q_p/Q_s ratio was 2.10 ± 0.16.

The end-diastolic volume/pressure ratios of the right ventricle were significantly higher than those of the normal children. The mean "distensibility" index was 18.5 ± 1.4 cm^3/m^2 per mm Hg compared with 12.7 ± 0.08 for the normal children ($P < 0.0005$). Similar data for the left ventricle obtained from nine subjects revealed a mean value of 5.49 ± 0.56 $cm^3/m^2/mm$ Hg compared with 7.2 ± 0.47 for the normal (P = not significant).

The mean left atrial maximal volume was 46.6 cm^3/m^2; this was significantly greater than the predicted normal value of 35.9 cm^3/m^2 ($P < 0.001$). This difference is evident in Figure 5 (left) where the observed and corresponding predicted normal values have been plotted against body surface area.

The relative changes in all three chambers are summarized in Figure 6 (left). These were expressed as percent observed/predicted normal values and were plotted against the angiographically derived pulmonary/systemic flow ratio (Q_{RV}/Q_{LV}). As shown by the respective regression lines, the right ventricle remained large and increased further with increasing shunts. In contrast, left ventricular size tended to be low normal with small shunts and decreased at Q_{RV}/Q_{LV} ratios of >2.0. Left atrial size was increased, and also tended to increase further with increasing shunts.

Left Ventricular Volume Overload (Patent Ductus Arteriosus)

The changes in the end-diastolic volume of the ipsilateral left ventricle and contralateral right ventricle are shown in Figure 7, in which the observed and predicted normal values are plotted against body surface area. The regression lines indicate that the left ventricle was significantly enlarged. The mean end-diastolic volume was 86.96 ± 4.86 cm^3/m^2 compared with the predicted normal value of 63.0 ± 2.35 ($P < 0.001$). By contrast, the contralateral right ventricle (mean 68.3 ±

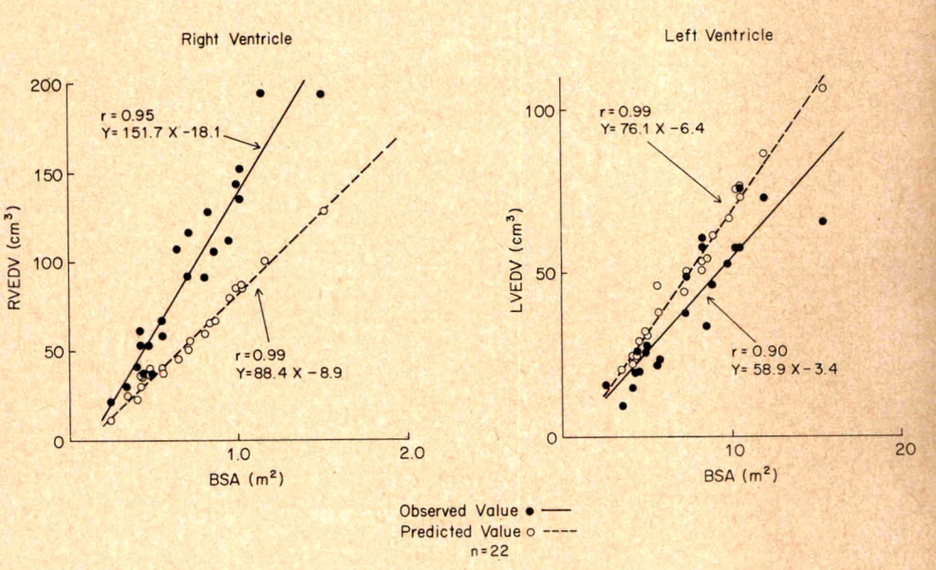

FIGURE 4. Right and left ventricular end-diastolic volumes (RVEDV and LVEDV) plotted against body surface area (BSA) in atrial septal defect. The predicted normal for each observed value, using the equations in Table IV for derivation, has also been plotted for comparison. The **solid line** is the regression line of the observed values and the **dashed line** that of the predicted normal values.

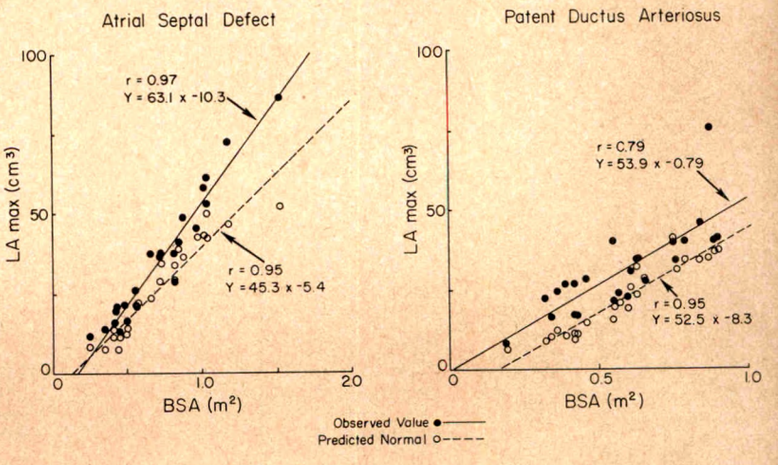

FIGURE 5. Maximal left atrial volume (LAmax) plotted against body surface area (BSA) in atrial septal defect **(left)** and patent ductus arteriosus **(right).** The predicted normal value for each observed value, derived from the equations in Table IV, is also shown. The **solid line** shows the regression of the observed values and the **dashed line** that of the predicted normal values.

2.95 cm^3/m^2) did not differ in size from the predicted normal value (mean 69.4 ± 2.48, P = not significant). The ejection fraction of the left ventricle was 0.67 ± 0.01 and that of the right ventricle 0.55 ± 0.02. Neither differed significantly from the normal value.

Left atrial enlargement was observed as expected (Fig. 5, right). The mean left atrial maximal volume was 52.5 ± 2.65 cm^3/m^2 compared with the predicted normal value of 36.2 ± 1.66 (P <0.001).

Systemic blood flow was derived from the angiographically estimated right ventricular output (Q_{RV}), and pulmonary blood flow from the angiographically estimated left ventricular output (Q_{LV}). The reverse relation occurs in atrial septal defect. The mean left ventricular output was 6.63 ± 0.39 liters/min per m^2, and the mean right ventricular output 4.17 ± 0.18. Good correlation was also observed between the angiographically derived pulmonary or systemic blood flow and those obtained by the Fick method in spite of assumed oxygen consumption values for the latter determinations (Table IV). The mean Q_{LV}/Q_{RV} ratio was 1.59 ± 0.09 compared with the Fick Q_p/Q_s of 1.97 ± 0.16 (P = not significant). Unlike the contralateral left ventricle in atrial septal defect, which demonstrated reduced output, the contralateral right ventricle in patent ductus arteriosus had an output that did not differ from the predicted normal value of 4.41 liters/min per m^2.

The end-diastolic volume/pressure ratios of the right ventricle were also analyzed and compared with those of the normal children. The mean "distensibility" index of the right ventricle was 10.41 ± 0.65 cm^3/m^2/mm Hg. This was lower than the normal value (12.7 ± 0.8 cm^3/m^2 per mm Hg) but not significantly so. The mean distensibility index of the left ventricle of six children, in whom it could be determined, was 11.3 ± 2.1 cm^3/m^2

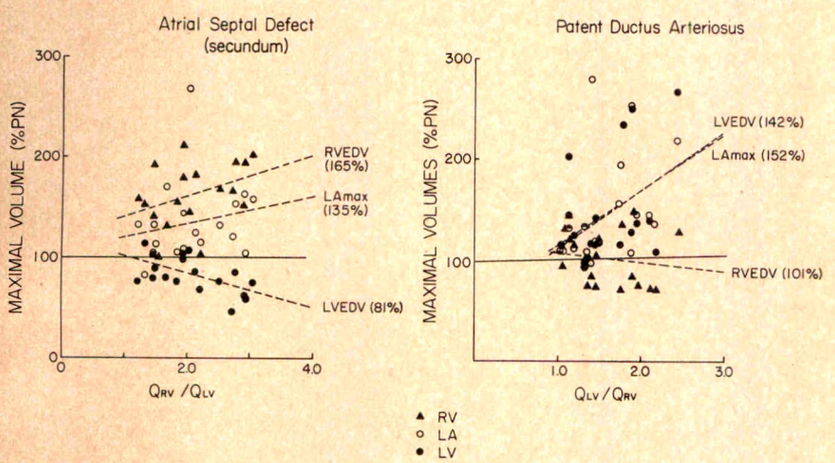

FIGURE 6. Summary of volume changes in the three cardiac chambers in atrial septal defect **(left)** and patent ductus arteriosus **(right).** Volumes were expressed as percent of the predicted normal (% PN), and were plotted against the angiographically derived pulmonary to systemic flow ratios (Q_{RV}/Q_{LV}). Regression lines are shown; the numbers in parentheses represent mean values. LA = left atrium; LAmax = left atrial maximal volume; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; RV = right ventricle; RVEDV = right ventricular end-diastolic volume.

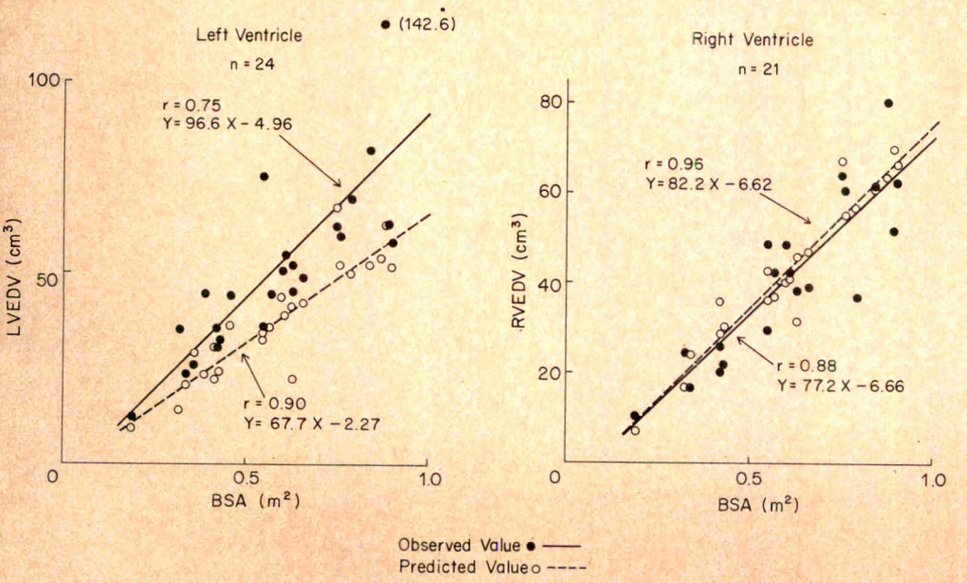

FIGURE 7. Right (RVEDV) and left (LVEDV) ventricular end-diastolic volumes plotted against body surface area (BSA) in patent ductus arteriosus. Corresponding predicted normal values, derived from equations in Table IV, are shown. The regression lines of the observed and normal values are also shown.

per mm Hg. This was significantly higher than the normal (7.2 ± 0.47 cm^3/m^2 per mm Hg, $P < 0.0025$).

The changes in the three chambers are also summarized in Figure 6 (right) and have been plotted against the angiographically derived pulmonary/systemic flow ratios. As shown by the superimposed left ventricular and left atrial regression lines, the degree of enlargement of both chambers relative to shunt flow was similar. The size of the contralateral right ventricle remained normal.

Discussion

The usefulness of a multivariable regression formula for predicting normal cardiac chamber size has been previously shown[4,6,9,14] and is again demonstrated. In this approach, the age, body size and heart rate are taken into consideration in interpreting the relative magnitude of the calculated volumes. None of the children in our control group (used for deriving the predicting formulas) had any demonstrable cardiac abnormality. This rigid approach was adopted since we have observed abnormal chamber volumes even in small shunting defects or mild valvular insufficiency (data in preparation). For the same reason, children with surgically corrected cardiac defects were excluded from this group.

This approach assumes that body size (height or weight, or both, relative to age) follows the same distribution curve as that of the normal (control) population. This is not necessarily true for patients with severe heart disease, in which case the predicted normal values may become spuriously high or low. None of the subjects in our two study groups had a body size outside the normal range.

Normal Values

Ventricular volumes: As in previous studies,[5,7,8,14] the end-diastolic volumes of the right ventricle were greater than those of the corresponding left ventricle in the normal children. This difference may be related to the normally greater distensibility of the right than the left ventricle. Greater right atrial than left atrial volumes have also been observed in normal children and have been explained similarly.[8] On the other hand, other studies,[6] using different methods for right and left ventricular volume calculation, have shown similar end-diastolic volumes for both chambers. This discrepancy, although disturbing, is not critical provided that the observed values by any method have appropriate controls by that method, such as the predicted normal volumes derived from legitimate regression equations.

Ventricular distensibility: The comparable "distensibility" of the right and left ventricles in the newborn period is consistent with the circulatory dynamics in utero. Thereafter, the diastolic volume/pressure relations of both ventricles increase, that of the right ventricle being significantly greater. The most rapid change occurs during the 1st year when a significant reduction in pulmonary vascular resistance is observed. Our observations agree with the animal data of Romero et al.,[16] which have shown comparable pressure-volume relations of the fetal right and left ventricles, greater right than left ventricular distensibility after birth, and greater distensibility of the ventricles in the adult than in newborn subjects.

The increase in ventricular and atrial distensibility with age appears to be mostly a function of the increase in chamber volumes since no corresponding changes in filling pressures were observed in our subjects. The precise mechanism that promotes this age-related change in wall compliance is not known. It has been suggested that the relatively increased amounts of noncontractile cellular elements including surface membranes in the young heart may contribute to the latter's reduced distensibility.[16] Alterations in myocardial connective tissue concentration may also be responsible. Myocardial hydroxyproline concentrations have been shown to be greater in the right heart chambers than in the corresponding left chambers, and in the atria than in the ventricles.[17] We have also observed, in studies on Wistar rats ranging in age from 1 day to 46 weeks (data in preparation), a progressive increase in left ventricular hydroxyproline concentration. It is thus possible that the increment in myocardial connective tissue concentration is a normal response of the heart to the increase in volume load accompanying body growth, and that similar changes occur in the volume-overloaded right ventricle in atrial septal defect or left ventricle in patent ductus arteriosus. This assumption remains to be proved. Other studies have also shown increased left ventricular distensibility in patients with mitral regurgitation.[18,19]

Ventricular Overloading

The right ventricular enlargement in atrial septal defect and the left atrial as well as left ventricular enlargement in patent ductus arteriosus are predictable changes. Previous studies have also demonstrated in-

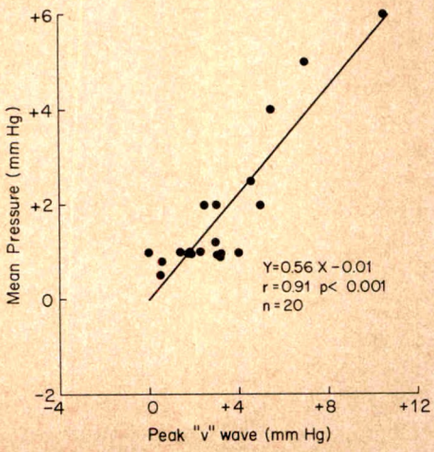

FIGURE 8. Relation of left to right atrial mean pressure gradient to peak V wave pressure gradient in secundum atrial septal defect.

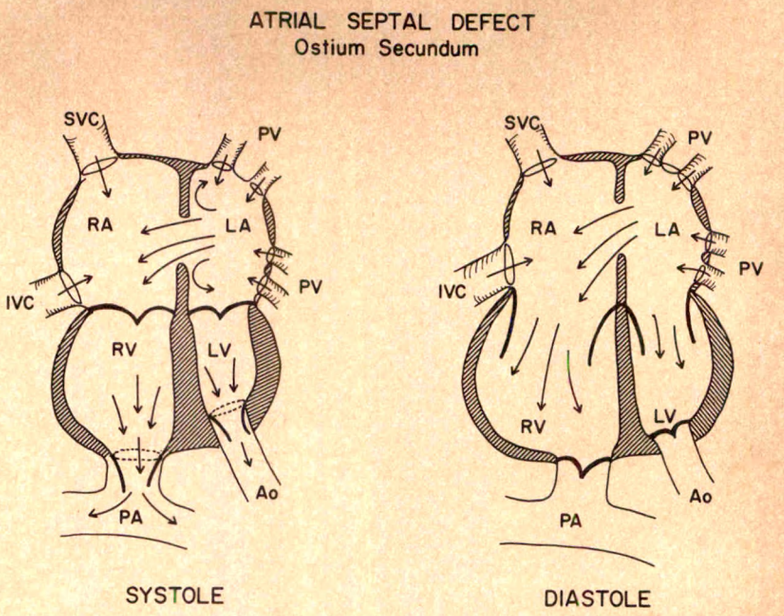

FIGURE 9. Schematic diagram of atrial shunting during ventricular systole while the atrioventricular valves are closed **(left)**, and during diastole while the atrial and ventricular chambers are in free communication **(right)**. Ao = aorta; IVC = inferior vena cava, LA = left atrium; LV = left ventricle; PV = pulmonary vein; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

creased volumes of the right ventricle[6,7] and right atrium[12] in atrial septal defect. The comparable enlargement of the left atrium and left ventricle in our subjects with patent ductus arteriosus reflects an identical response to the volume load.

Left atrial enlargement of atrial septal defect: The pathogenesis of the left atrial enlargement accompanied by reduced left ventricular size and systemic output in secundum atrial septal defect is unclear. The atrial enlargement suggests that the septal defect, although usually large, may still be somewhat functionally restrictive to transseptal flow. Analysis of the atrial pressures in our patients recorded during catheter pullback from the left to the right atrium supports this view. The mean pressure gradients ranged from 0.5 to 6 mm Hg, and these correlated well with the peak V wave pressure differential between the two atria (Fig. 8), indicating inadequate pressure equilibration between the two atrial chambers. Levin et al.[20] have also demonstrated consistent left to right atrial pressure gradients during the latter half of ventricular systole, especially at the peak of the atrial V wave and during atrial contraction. Cineangiocardiographic analysis demonstrated major left to right shunting at these critical periods. Our hypothesis assumes that the left to right atrial shunt during ventricular systole is not large enough to counterbalance the increased pulmonary venous return to the left atrium at this phase of the cardiac cycle. This would favor enlargement of the left atrial chamber. The enlargement of the right atrium,[12] even to a greater extent than that of the left, does not necessarily contradict this concept.

Small left ventricle in atrial septal defect: The tendency for the left ventricle to become small is likewise not paradoxical to this assumption. During ventricular diastole, the left atrium empties into the left ventricle as well as into the right atrium-right ventricle by way of the septal defect. Since the left ventricle is less distensible than the combined right heart chambers, preferential flow to the latter is favored, with consequent reduction in left ventricular filling. The diagrams in Figure 9 illustrate our hypothesis. The reduced left ventricular ejection fraction and low systemic output observed in this condition would be consistent with this concept of reduced left ventricular preload.

Left ventricular dysfunction in atrial septal defect: We have no data concerning the effects of increasing age upon the left heart changes in atrial septal defect since we did not perform serial hemodynamic studies. However, recent studies in adult patients with this disease have also demonstrated evidence for left ventricular dysfunction in the form of reduced end-diastolic volume, stroke volume and output.[21] There is, therefore, sufficient evidence to suggest that the usual practice of delaying surgery for several years may not be the best policy in the management of this disease. The impaired cardiac output response to exercise of adult patients who have had total repair of atrial septal defect[22] could very well be a reflection of the left heart dysfunction already present before surgery.

Right ventricle in patent ductus arteriosus: Unlike the left ventricle in atrial septal defect, the right ventricle in patent ductus arteriosus is normal. This difference in response of the contralateral ventricles in the two entities may be related to the level of the shunt; in atrial septal defect it is proximal to the contralateral ventricle, whereas in the latter it is distal to it. Left to right shunting occurs before and during ventricular filling in atrial septal defect, but after ventricular filling in patent ductus arteriosus. The systemic output and the right ventricular preload in the latter remain normal.

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Fetal and Infant Death, Twinning and Cardiac Malformations In Families of 2,000 Children With and 500 Without Cardiac Defects

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Analysis of family data on 2,000 children with a congenital cardiac malformation of unknown origin and 500 with an innocent murmur showed the incidence of twinning in probands, siblings and parents to be the same as in the general population. The mothers in the two groups of probands had the same incidence of spontaneous abortions and stillbirths. There was a small increase in infant mortality in siblings of probands with a cardiac malformation, but this could be accounted for by the increased incidence of cardiac malformations. The latter occurred in 1.4 percent of all siblings and in 1.7 percent of later born siblings. Complete concordance for malformation type occurred in 31 percent of affected siblings and 46 percent of affected parents, and partial concordance occurred in an additional 21 and 8 percent, respectively. Combined direct and indirect observations and calculations indicate that the risk of recurrent cardiac malformation is 1.4 to 3 percent in families in which one child was born with a cardiac malformation of unknown origin; no significant difference was evident for the various cardiac malformations.

The etiology of congenital heart malformations continues to be the subject of numerous studies, but the emphasis has shifted from unselected population studies to the identification of defects or syndromes caused by specific genes, chromosomes or environmental factors. In the majority (80 to 90 percent) of patients with a congenital heart defect, no underlying causative factor or syndrome can be identified. The present study was limited to this group of patients, with the following objectives: to evaluate malformations separately; to investigate reproductive loss in the mothers (stillbirths and spontaneous abortions); to examine infant mortality in siblings; to evaluate the incidence of twinning in patients and their siblings and parents; to determine the incidence and types of cardiac malformations in siblings and parents; and to compare these data with "expected" data, data in a group of patients with innocent murmurs and data reported by others.

Materials and Methods

Case material: Data were obtained during the 21 years from 1953 to 1973 in the Pediatric Cardiac Clinic of the University of Minnesota Hospitals and were reviewed and updated in 1973 and 1974. I personally obtained the family history and examined the children. For patients with a cardiac malformation, confirmatory information was regularly available from cardiac catheterization, surgery or autopsy studies, except for a few patients whose clinical and laboratory findings were considered diagnostic of isolated defects such as ventricular septal defect or valvular pulmonary or aortic stenosis. The majority of patients were born in Minnesota, but a significant number were from North and South Dakota and a scattering from western Wisconsin and northern Iowa. Nonwhites constituted less than 1 percent of cases.

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Approximately 25 percent of the patients initially seen were excluded because there was evidence or suspicion of a specific causative factor. Thus, all patients with known or suspected chromosomal defects were omitted, as were patients with entities caused by a single gene, patients with syndromes or multiple defect complexes of unknown origin and entities probably due to a single gene (for example, Noonan's syndrome, Leopard syndrome, dysplastic pulmonary valve stenosis, Kartegener's syndrome, Holt-Oram syndrome and DiGeorge syndrome), together with patients born of pregnancies complicated by rubella, diabetes or anticonvulsant therapy. Patients with endocardial fibroelastosis, supravalvular aortic stenosis, peripheral pulmonary arterial stenosis, prolapsing mitral leaflet and tumors were also excluded. Only the first seen of affected siblings was designated a proband, whether earlier or later born. Simultaneously, comparable data were obtained on 500 children whose only finding was an innocent-sounding venous hum, lower left sternal border vibratory murmur or soft pulmonary flow murmur. A third group of 70 patients with Down's syndrome was also included for comparison and, although the data are limited, they may be of use to others interested in this condition.

Only those cases of congenital heart malformation were included in which maternal age at the time of the birth of the child had been obtained, but some cases without this information were included in the innocent murmur group. Information on twinning was unavailable for some parents in all three groups. Half-sibs were omitted in the tabulations. Data published earlier[1] on patent ductus arteriosus were not included in this study. Pregnancies terminating in the 1st 5 months were classified as abortions; all stillborn fetuses or infants born beyond this time were classified as stillbirths and were regularly identified as to sex and weight. All abortions were reported by the mothers as spontaneous.

Classification of malformations: Common malformations were tabulated separately and the others were grouped as "isolated uncommon malformations" or as "multiple malformations." Patients with nonvalvular aortic stenosis, aortic atresia, infundibular pulmonary stenosis or pulmonary atresia were placed in the "isolated uncommon malformation" group. Atrial septal defects included cases of both the secundum and sinus venosus type. Cases of coarctation of the aorta with a nonstenotic bicuspid aortic valve were classified as coarctation. Cases listed as transposition of the great vessels were all of the "complete" type (*d*-loop) and included cases with and without ventricular spetal defect and pulmonary stenosis.

Expected data: To obtain "expected" data, for comparison with observed data, the following procedures were followed. The pregnancies of the mothers were grouped according to maternal age at the time of birth, and the data of Myrianthopoulos and associates[2] on twinning in pregnancies of white mothers were used to calculate the expected number of twins or sets of twins among the probands and their siblings in each maternal age group. To obtain the expected number of stillbirths (fetal death after 20 weeks' gestation) and the expected number of infant deaths among siblings, data from the Minnesota Department of Health were used.[3] Stillbirths and live births were tabulated according to the year of birth, and the expected number of stillbirths was obtained by applying the appropriate stillbirth rates to the yearly numbers of total births. The expected number of infant deaths was obtained by applying the appropriate infant mortality rates to the yearly numbers of live births. The calculation of expected number of cases of congenital heart malformations in siblings was based on the value of 0.767 percent reported for live births

TABLE I
Incidence of Twinning and Cardiac Malformations in Probands, Siblings and Parents

	Probands			Siblings							Parents				
							With CM								
Diagnosis	Cases (no.)	Twins Obs	Twins Exp	Sets of Twins Obs	Sets of Twins Exp	Live-born	Obs	Exp	Diagnosis Known	Diagnosis Concordant	Total	With CM*	Diagnosis Concordant	With Data on Twinning	Twins
VSD	572	7	12.82	16	14.97	1,396	29	. . .	23	7	1144	3	2	932	18
ASD	145	4	3.55	6	4.84	425	3	. . .	2	1	290	1	1	250	5
PDA	118	3	2.64	4	3.39	311	3	. . .	3	2	236	4	3	152	1
CA	122	5	2.83	2	3.59	328	2	. . .	2	1	244	5	1	218	3
PS	180	9	4.36	4	6.04	528	8	. . .	5	3	360	3	2	288	7
AS	157	3	3.85	9	5.70	515	4	. . .	4	1	314	2	0	244	8
ECD	48	0	1.11	3	1.48	132	2	. . .	2	1	96	1	1	74	0
TGV	69	0	1.59	1	1.30	127	0	. . .	0	0	138	0	0	118	0
TF	214	6	4.92	5	6.48	584	9	. . .	8	3	428	2	1	322	6
ID	118	4	2.73	1	3.07	277	4	. . .	3	0	336	0	0	192	4
MD	257	6	6.02	4	8.11	716	12	. . .	9	0	514	3	0	412	6
Total	2000	47	46.42†	55	58.97	5,339	76 (1.4%)	41.0	61	19	4000	24	11	3202	58 (1.8%)
Innoc	500	10	. . .	14	. . .	1,125	11 (1.0%)	8.6	. . .	. . .	1000	0	. . .	408	9 (2.2%)
	441‡	9	10.20	11	11.09										
DS	70	0	0.96	1	2.48	216	1	1.7	1	1	140	0	0	116	0

* Type of malformation known in all cases.

† Twins have a higher fetal and neonatal death rate than singletons,[2] thereby reducing their incidence in the pediatric population from which patients with cardiac malformations are drawn. Thus, on the basis of the additional 10 percent mortality noted in non-proband twins in the present study, the expected number should be reduced to 41.78, still not significantly different from the observed value.

‡ Maternal ages needed for calculating expected number of twins available for only 441 mothers.

AS = aortic stenosis; ASD = atrial septal defect; CA = coarctation of aorta; CM = cardiac malformation; Conc = concordant; DS = Down's syndrome; ECD = endocardial cushion defect; Exp = expected; ID = isolated uncommon defects; Innoc = innocent murmur; MD = multiple defects; Obs = observed; PDA = patent ductus arteriosus; PS = pulmonary stenosis; TF = tetralogy of Fallot; TGV = transposition of great vessels; VSD = ventricular septal defect.

by Mitchell et al.[4] Twin births included both live-born and stillborn. Abortions were listed as single events even if multiple concepti were thought to have been involved. No information was obtained on the presence or absence of cardiac malformations in stillborn infants. The twin partners of probands are not included in the overall compilation of siblings but are discussed in the text.

The average maternal age at the time of birth of probands with a cardiac malformation was 26.58 years, and of probands with an innocent murmur or Down's syndrome 26.87 and 30.54 years, respectively.

Results

Twinning: Data concerning the incidence of twinning in probands, siblings and parents are shown in Table I. In the group with an innocent murmur, twinning data were limited to the 441 cases with a recorded maternal age. The incidence of twins in probands and siblings closely approximated the expected incidence in all three patient groups. Likewise, the incidence rate of twins among the parents in all groups was similar to the rate of 2 percent that would be expected from a twinning incidence rate of 1 percent in the population.

The 47 twin partners of probands with a cardiac defect were all live-born, but 2 died in infancy. Only one had a cardiac defect, and this was a discordant defect occurring in an unlike-sex partner. Two of the 10 twin siblings of probands with an innocent murmur were stillborn, but none of the other 8 died or had a cardiac defect.

Incidence and concordance of cardiac malformations in siblings and parents: The observed number of 76 cases (1.4 percent) of cardiac malformation in siblings of probands with a cardiac defect was significantly higher than the 41 expected ($P < 0.05$) (Table I). The incidence was greater than in the sibling group with an innocent murmur, but not significantly so, the population of the latter group being relatively small. The incidence rate of cardiac malformations in siblings of probands with an affected parent was 6.8 percent (2 in 34 siblings whose mother was affected and 2 in 25 whose father was affected) compared with 1.4 percent (72 in 5,280) when neither parent was affected. This difference was significant ($P < 0.005$) after correction for sample size. The corresponding figures for later born siblings were 25 percent (3 in 12) and 1.5 percent (26 in 1,700). In siblings of probands with an innocent murmur, the incidence of cardiac malformations was slightly, but not significantly, greater than expected (Table I). The incidence of cardiac malformations in parents of probands with cardiac defect was significantly greater than in parents of probands with an innocent murmur ($P < 0.02$). Of the 61 siblings whose cardiac defect could be identified, 19 had a defect that was the same as that in the proband, 13 had one component in common and 29 had a completely discordant defect. Of the 24 affected parents, 11 had a concordant defect, 2 had one component in common and 11 had a completely discordant defect.

Outcome of other pregnancies of mothers: Table II shows data pertaining to the outcome of all other pregnancies of the mother, with a separate listing for those occurring after birth of the proband. The incidence rate of spontaneous abortions was not significantly different in the three groups for total or later pregnancies, although the figures tended to be slightly higher for the cardiac malformation group. However,

TABLE II

Outcome of Other Pregnancies of Mothers

	All Pregnancies					Later Pregnancies						
				Stillbirths							Offspring With Cardiac Malformations	
Proband Diagnosis	Total no.	Spontaneous Abortions	Total Births	Obs	Exp	Total no.	Spontaneous Abortions	Still-births	Births	Infant Deaths	Obs	Exp
VSD	1,626	231	1,411	15	19.38	528	74	1	453	8	9 (2.0%)	...
ASD	513	89	430	5	6.21	166	30	1	135	4	0	...
PDA	374	60	318	7	4.51	116	17	3	96	2	1 (1.0%)	...
CA	378	50	330	2	4.58	132	16	0	116	3	2 (1.7%)	...
PS	631	98	537	9	7.81	204	33	4	167	1	0	...
AS	617	107	519	4	7.74	233	44	1	188	6	3 (1.6%)	...
ECD	163	30	136	4	1.89	54	7	1	46	3	0	...
TGV	152	26	127	0	1.66	16	0	0	16	0	0	...
TF	669	90	584	0	8.31	219	33	0	186	4	5 (2.7%)	...
ID	327	47	281	4	3.94	72	12	2	58	2	0	...
MD	853	139	718	2	9.90	289	38	0	251	7	9 (3.6%)	...
Total	6,303*	967 (15.3%)	5,391	52	75.93	2,029	304 (15.0%)	13	1,712	40	29 (1.7%)	13.1
Innoc	1,307†	182 (13.9%)	1,139	14	17.02	467	59 (12.7%)	0	408	8	5 (1.2%)	3.1
DS	244‡	27	218	2	3.22	20	1	0	20	1	0	0.1

* Also 14 ectopic pregnancies and 4 hydatidiform moles.
† Also 5 ectopic pregnancies.
‡ Also 1 ectopic pregnancy.
Abbreviations as in Table I.

the incidence rate of stillbirths was significantly lower than expected in the cardiac malformation group but was not significantly different from the rate in the innocent murmur group, in which the observed rate was also lower than expected, though not significantly so. In the cardiac malformation group there were 14 ectopic pregnancies and 4 hydatidiform moles; in the innocent murmur group there were 5 ectopic pregnancies, and in the Down's syndrome group there was 1 such pregnancy. The incidence rate of cardiac malformations was slightly higher, but not significantly so, in siblings born after the birth of the proband with a cardiac defect than among siblings born earlier (1.7 versus 1.3 percent).

Infant mortality in siblings: Table III shows data relative to infant mortality in siblings and the causes of death. No significant differences were noted between observed and expected values for infant deaths or between observed values in the three groups. As mentioned, there was an excess of 35 cases of cardiac malformation in siblings (76 observed minus the 41 expected). According to the infant mortality rate noted in siblings with a cardiac malformation (7 of 23 or 30 percent), 10.5 deaths would be expected in this group. The addition of 10.5 to the otherwise expected 132.25 gives a total of 142.75, which is practically identical to the observed value of 142.

Discussion

Studies relating to the familial incidence of congenital cardiac malformations are handicapped by several factors. The low incidence rate of congenital cardiac malformations, particularly as individual defects, both in the general population and among relatives of affected subjects, necessitates very large population samples to achieve statistical significance. Thus, tests of statistical significance have rarely been applied to the data obtained in family surveys. Moreover, the exact diagnosis may be impossible to ascertain except by autopsy, the cardiac malformation may change with time and relatives may die or be impossible to locate or be uncooperative. Data were therefore sought in this study that would minimize or be largely independent of these factors. Thus, information on twinning, maternal and sibling birth dates and date of death of siblings was easily recalled by mothers. Without examining all parents and siblings, one would expect some cases of cardiac malformation to be missed. However, a significant number of missed cases in siblings would be evidenced by an easily identified increase in infant mortality in siblings.

Twinning

The incidence of twinning in probands, either with or without cardiac malformations, and in their siblings and parents, was found to approximate that in the general population. No comparable published data are available, although in one study the incidence rate of twins in patients with a cardiac malformation was 4.4 percent (20 of 457),[5] but the data were not adjusted for maternal age or classified as to live-born or stillborn status. In a series of 92 patients with atrioventricular canal defect, 6 twins were found,[6] but in that report and others the samples were too small to warrant the conclusion that twinning itself predisposes to congenital heart malformations. The present data instead support the tenet that twinning does not predispose to cardiac malformations and indicate that twinning is neither increased nor decreased among the immediate relatives of patients with cardiac malformations. The possibility of an increased incidence rate of twins in stillborns with a cardiac malformation has not been excluded by this study since data on this point were not obtained.

The incidence of cardiac defects in twin partners of probands with a cardiac defect (1 in 47) was much smaller than that reported by others[7] and will be dealt with in a separate publication.

TABLE III

Infant Mortality and Causes of Infant Death Among Siblings

Proband Diagnosis	Live-born Siblings	Infant Deaths Among Siblings		Causes of Death								
		Obs	Exp	Pre-maturity	Malformations: Cardiac	Malformations: Other	Pulmonary Complications	Infections	Birth Injury	"Crib Death"	Misc.	Unknown
VSD	1,396	30	31.72	12	7	5	2	1	1	1	1	0
ASD	425	19	19.11	10	1	1	2	1	0	1	1	2
PDA	311	16	7.02	4	1	1	2	0	2	0	5	1
CA	328	7	7.54	3	1	0	0	1	0	1	0	1
PS	528	11	12.35	1	2	2	1	1	0	1	1	2
AS	515	15	12.42	4	2	3	2	2	0	0	1	1
ECD	132	8	3.05	0	2	2	1	1	2	0	0	0
TGV	127	1	2.67	0	0	0	0	0	1	0	0	0
TF	584	10	13.73	2	1	3	3	0	0	0	0	1
ID	277	9	6.34	0	3	1	3	1	0	0	1	0
MD	716	16	16.30	7	3	1	2	0	1	0	1	1
Total	5,339	142	132.25	43	23	19	18	8	7	4	11	9
Innoc	1,125	27	27.14	8	6	2	1	2	2	1	4	1
DS	216	9	5.21	1	1	4	0	1	0	0	1	1

Misc. = miscellaneous; other abbreviations as in Table I.

Spontaneous Abortions

No significant difference in the incidence of spontaneous abortions was found between mothers of probands with or without a cardiac malformation. The figure of 14 to 15 percent is similar to that reported by others for pregnancies in the general population[8,9] and for mothers of children with a cardiac malformation.[9]

Stillbirths

A significantly lower than expected incidence rate of stillbirths was found in groups with and without a cardiac malformation on the basis of Minnesota Department of Health data.[3] The latter showed a decreasing incidence rate of stillbirths from about 3 percent in 1930 to 1 percent in 1970. It is possible that in earlier years some late abortions or natal deaths were reported on birth certificates as stillbirths. In the present study, the overall incidence rate of stillbirths in the cardiac malformation group was 0.96 percent, with a rate of 1.02 percent for the 1,957 births before 1956 and 0.93 percent for the 3,434 births since 1956. In the innocent murmur group the overall incidence rate was 1.23 percent, with 0.72 percent for the 555 births before 1956 and 1.71 percent for the 584 births since 1956. These latter values are not significantly different, the sample sizes being relatively small. Inasmuch as the incidence of stillbirths was essentially the same in the cardiac malformation and innocent murmur groups, it would seem unjustified to attribute clinical significance to the variance from the Department of Health figures. The incidence rate of stillbirths has been reported as high as 2.4 percent in a recent general population survey[4] but has usually been found to approximate 1.0 to 1.5 percent in both the general population[9] and in families ascertained by the birth of a child with a cardiac or noncardiac malformation.

Infant Mortality in Siblings

As noted earlier, infant mortality in siblings of probands with a cardiac malformation was slightly greater than expected, but not significantly so, and the slight surplus was of the magnitude expected from the increased number of congenital cardiac malformations. Aside from this excess of deaths due to cardiac malformation, the causes of death were similar in number and type to those in the innocent murmur group and in the general population.

Congenital Cardiac Malformations

The incidence of cardiac malformations was significantly greater than expected among siblings of probands with a congenital cardiac malformation. As mentioned, data on infant deaths in siblings were obtained to assess the accuracy of the reported incidence of cardiac malformations in siblings. Approximately 30 percent of infants with congenital cardiac malformations die by age 1 year, as found in this study and that of others.[4] An increase in the incidence of congenital cardiac malformations in any population should therefore be accompanied by an increase in infant mortality. In the present study, the overall incidence rate of cardiac malformations in siblings was 1.4 percent, compared with an expected rate of 0.77 percent.[4] There was a slight but not significant increase in infant mortality in siblings, and this paralleled the increased number of siblings with a cardiac malformation. For the sample size used, a significant increase in infant mortality would have occurred only if the incidence rate of a cardiac malformation had reached 3 percent in siblings. Thus, an additional 2.23 percent of cardiac malformations (the difference between 3 percent and the 0.77 percent figure in the general newborn population[4]), coupled with a 30 percent infant mortality rate for such patients, would have resulted in 36 additional infant deaths, a number that would be significant for a group of 5,339 live-born infants. The incidence rate of cardiac malformation in siblings of patients with a cardiac malformation of nonspecific origin thus should lie between the observed value of 1.4 percent and the maximal value of 3 percent and probably be closer to the former than to the latter value.

This discussion, like that of most published studies, has concerned the incidence of cardiac malformations in all siblings. However, the manner and degree of ascertainment of cases in the population affects the results. This bias can be minimized by limiting the analysis to pregnancies occurring after the birth of the proband. As shown in Table III, the incidence rates of cardiac malformation among later born siblings was 1.7 percent, which is slightly greater than the overall incidence rate of 1.4 percent and the 1.3 percent incidence rate in earlier born siblings.

Genetic Implications

Congenital cardiac malformations are commonly viewed as a single categorical diagnosis or as a group of discrete entities. Actually, they constitute a hodgepodge of malformations with but one feature in common: They involve the heart or great vessels. However, individual cardiac malformations do appear to be at least partially causally related inasmuch as they occur together in one person or separately in close relatives more often than chance would dictate (for example, ventricular septal defect and infundibular pulmonary stenosis). Individual malformations can show racial or geographic differences with respect to incidence[10] or structural detail[11] and can be characteristic features of syndromes due to gross chromosomal defects or to a single gene.

Multifactorial inheritance concept: The current concept is that cardiac malformations are quasicontinuous threshold traits resulting from the interaction of multiple genes with numerous environmental factors (multifactorial inheritance).[12] According to this interpretation, the incidence of a malformation in first degree relatives (siblings and offspring) has been considered to be equal to the square root of the incidence rate of the malformation in the general population.[13] Therefore, if the incidence rate of congenital cardiac malformations is 0.8 percent, the square root of it would be 9.0 percent, a figure much higher than ever reported for cardiac defects in first degree relatives. Consequently, it is clear that a single multifactorial trait is not

involved. The square root principle has therefore been applied instead by others to individual cardiac malformations, but without exclusion of cases involving known genetic or environmental factors. Unfortunately, although polygenic inheritance does indeed presuppose a variety of genes of various levels of dominance, the inclusion of cases of known specific origin in the overall group for genetic or statistical analysis will tend to obscure rather than illuminate etiologic mechanisms.

As previously emphasized, the present study was limited to patients whose malformations were clearly of unknown origin. There is thus some question as to whether multifactorial inheritance concepts can be applied in the same manner as used by others for the entire population with a cardiac malformation. Other questions in analysis also arise. Thus, if the proband is identified as having a specific defect, should one count all recurrences of cardiac malformation, regardless of type? If the recurrent case involves multiple defects, one of which is present in the proband, should it be counted? If cardiac malformations are to be treated as separate entities when identifying probands, should they not also be viewed as separate entities when tabulating recurrences? Exclusion of recurrences in subjects with clearly different anatomic features will result in a lower recurrence rate and a deviation from the calculated and observed rates reported by others. On the other hand, exclusion of cases that represent an overwhelming one-time environmental insult (such as rubella infection in pregnancy) will act in the opposite direction.

The recurrence rate of 1.7 percent in later born siblings of probands with cardiac malformations of unknown origin in this study is similar to that reported by Mori et al.[14] in Japan (1.8 percent for cases exclusive of primary myocardial diseases), but lower than the 2.8 percent figure for all siblings as reported by Nora et al.[15] in the United States for unselected patients with cardiac defects. The latter workers found the incidence in siblings to correspond very closely to the square root of the incidence of the individual malformations in the general population; however, they included all cases of cardiac malformation among siblings, not just the malformation identical to that in the proband. Their data, although imposing in magnitude for this type of material, nevertheless do not demonstrate statistically significant differences between recurrence rates for the individual malformations (for example, ventricular septal defect versus aortic stenosis). In the present study, as in the report of Mori et al.,[14] the more common malformations did not have higher recurrence rates but the data are too limited to prove or disprove differences in recurrence rates.

The incidence rate of cardiac malformations in parents of probands with a cardiac malformation generally has been found to be lower than among siblings, since the potential pool of affected parents is reduced by the significantly lower life expectancy of patients with a cardiac malformation, a point well clarified by others.[15] In the present study, only 0.6 percent of parents (11 fathers and 13 mothers) were affected, as compared with 1.4 percent of all siblings. Comparable values from the studies of Nora et al. were 1.6 and 2.8 percent.[15] No data were obtained in the present study with regard to incidence in offspring, but Nora et al. reported a value of 3 percent, very similar to their value for siblings. Others have reported the incidence in offspring of affected mothers to be greater than 5 percent.[16]

Genetic and environmental factors in siblings, parents and offspring versus proband: If genetic factors are involved in the causation of cardiac malformations, defects occurring in siblings, parents and offspring should tend to be similar to that in the proband. Predisposing environmental factors would further this trend since they too can act to cause a familial aggregation of malformations. Although it seems unlikely that the genes and environmental factors predisposing to cardiac malformations are all specific in nature, the recurrent malformations in relatives indeed have shown a significant tendency to be the same as in the proband in this and other studies,[17] but not to the extent reported by others.[15] The present study showed complete concordance in 11 of 24 affected parents and in 19 of 61 affected siblings (there was partial concordance in an additional 2 parents and 13 siblings). This tendency to somewhat greater concordance between parent and child than between siblings was also present in the study by Ehlers and Engle.[17]

Concordance rate for specific cardiac malformations: If one assumes that the individual types of cardiac malformations are unrelated with regard to predisposing factors, then the first degree relatives should show other cardiac malformations in the same number as in the general population. If, instead, all cardiac malformations are considered to have the same, or most of the same, predisposing genetic and evironmental factors, then it is not valid to view them as etiologically distinct entities and to apply the square root principle to them individually. The true situation probably lies somewhere in between, but closer to the former, with some predisposing polygenes and environmental factors in common, but with enough variability that recurrences in close relatives will include both the gamut of cardiac malformations present in the general population plus a greater incidence of the malformation present in the proband than would be expected by chance.

Under these circumstances one would not expect more than a crude approximation of the recurrence rate to the values projected by the square root rule. Moreover, if predisposing genetic and environmental factors tend to be specific, then the concordance rate for recurrent malformations should be higher for relatives of probands with common defects, since recurrence rates would be expected to be higher and since the common malformations constitute a higher percentage of the entire population of cardiac malformations. Thus, in the absence of any predisposing factors, concordance of cardiac malformations in relatives of probands with a ventricular septal defect should be about 30 percent, which is the percentage of isolated ventricular septal defect among all cardiac malformations. On the other hand, in affected relatives of probands with such rare

defects as truncus arteriosus the concordance value would be closer to 1 percent. In each case, one would expect a total recurrence rate of about 0.8 percent, the incidence of cardiac malformations in live-born infants.[4] When predisposing genetic and environmental factors come into play, the concordance rates would be expected to rise, to a value of nearly 90 percent for ventricular septal defect and nearly 50 percent for rare cardiac defects, if one assumes that the square root rule is valid. Specifically, in the case of ventricular septal defect, the square root recurrence estimate of 5 percent would be added to the 0.55 risk for cardiac malformations other than ventricular septal defect (giving a concordance value of 5/5.55 or 90 percent), and for a rare defect such as truncus arteriosus the square root estimate of 0.7 would be added to the 0.8 risk of cardiac malformations other than truncus arteriosus (giving a concordance value of 0.7/1.5 or 47 percent). The absence of such a trend in the present study or in published reports weighs against the validity of the square root principle, either in interpreting or projecting recurrence rates for cardiac malformations.

In the present study, the cardiac malformation was identical to that in the proband in 7 of 13 affected mothers and in 4 of 11 affected fathers. No similar parental breakdown of data has been given by others, but further information on this point might help in the understanding of etiologic mechanisms.

Empiric Risk Figures

Generally, empiric risk figures have been based on the incidence of cardiac malformations in all siblings of affected probands, but it is preferable to base them on pregnancies subsequent to the birth of the proband. In the present study, this gave a risk figure of 1.7 percent, slightly higher than the overall figure of 1.4 percent. Through the use of infant mortality data in siblings an upper limit of 3 percent was established. The recurrence rates in siblings of probands with different malformations showed a great scatter, not unexpected for the sample sizes involved, even if true recurrence rates did range from 1 to 5 percent. This is in contrast to the data of Nora et al.,[15] who found exceedingly close approximations of observed and expected recurrence figures using the square root rule. However, the latter data were comparable in magnitude with those in the present study, and the differences between the recurrence rates for the individual malformations do not appear statistically significant. There are reports[16] that would suggest that the incidence of cardiac malformations may be greater in offspring than in siblings of probands with cardiac malformations, even apart from the effect that maternal factors such as hypoxia might have on the developing fetus.

Since the reports on recurrences of cardiac malformations in siblings do not deviate significantly from one another, and since statistically significant differences have not been shown between the various individual malformations, it seems reasonable to use either the 1 to 5 percent risk figures reported by Nora et al.[15] for individual malformations, or the 2 to 3 percent risk figure noted in this and other studies for all cardiac malformations. However, as noted, the risk figure must be increased, perhaps to 5 to 10 percent, once a second case has occurred in a sibship, and perhaps to 10 to 20 percent if a parent is also affected, since these features indicate stronger aggregations of predisposing genetic and environmental factors. An even greater risk is indicated if there are additional affected persons in the immediate family. Most important, different risk figures must be developed and used for situations in which a specific gene, chromosome or environmental factor can be identified, and it behooves the physician and counselor to examine each patient's clinical diagnosis and family history critically before expressing opinions on the risks for recurrence of a cardiac defect in the family.

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Postoperative Pathology of Congenital Heart Disease

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Complete and unselected data concerning the postoperative pathology of congenital heart disease are presented for the first time. This study was based on 2,365 autopsies performed at the Children's Hospital Medical Center, Boston, in the 9 years from 1966 through 1974. Of these, 586 autopsies (25 percent) revealed congenital heart disease—238 performed in medically treated patients (41 percent) and 348 in surgically treated patients (59 percent). Tetralogy of Fallot, including cases with pulmonary outflow tract atresia and other associated malformations, was the congenital heart disease most often encountered in the postoperative autopsy series (88 cases, 25 percent of that series). *D*-transposition of the great arteries, including cases with other associated anomalies, was second (54 cases, 15.5 percent). Early death (hospital mortality) accounted for 320 (92 percent) of the 348 surgical cases; late death occurred in 28 patients (8 percent). Causes of late postoperative death included arrhythmias, excessively small ventricular septal defect with tricuspid atresia, massive hemoptysis, rupture of the pulmonary artery, cyanotic spell, congestive heart failure and infection. Prophylactic penicillin is recommended for patients with the asplenia syndrome because of their probably enhanced vulnerability to fulminating septicemia by encapsulated bacteria such as the pneumococcus. Completeness and lack of selection in reporting data are essential in the interests of perspective and comparability of findings.

In a recent meeting on emerging problems in adults and children after cardiac surgery, Engle[1] posed the following difficult question: As assessed from the standpoint of cardiac pathology, what problems will patients with congenital heart disease encounter after cardiac surgery in the future? To consider this question, we thought it necessary first to establish our past postoperative problems. Hence, this presentation is concerned with both past problems and future projections.

In making this investigation, we found virtually no relevant reports. To our knowledge, comparable data have not been published previously. This finding in turn led us to appreciate how important it is that published data, whether pathologic findings or surgical results, be complete and unselected. Otherwise, it is not possible to make valid comparisons of data from different centers. Even within one center it is not possible to see an individual finding in accurate perspective unless the data are complete and unselected.

Case Material

A study was made of all autopsies performed in patients with congenital heart disease at the Children's Hospital Medical Center in Boston in the 9 years from 1966 through 1974. No case was omitted for any reason. During this time, 2,365 autopsies were performed. Of these, 586 revealed congenital heart disease.

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Findings

Frequency: The annual frequency of autopsy cases of congenital heart disease ranged from a low of 21 percent of all autopsies performed in 1967, to a high of 29 percent in 1969 (average 25 percent from 1966 through 1974, Fig. 1, Table I).

Medical versus postsurgical autopsies: *Medically treated patients,* who underwent no cardiovascular surgery, ranged from a low of 29 percent of all autopsy cases of congenital heart disease in 1974 to a high of 50 percent in 1970 (average 41 percent from 1966 through 1974, Fig. 2, Table I).

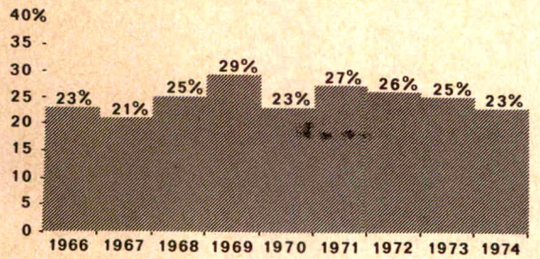

FIGURE 1. Autopsy cases of congenital heart disease expressed as percent of all autopsies in each year.

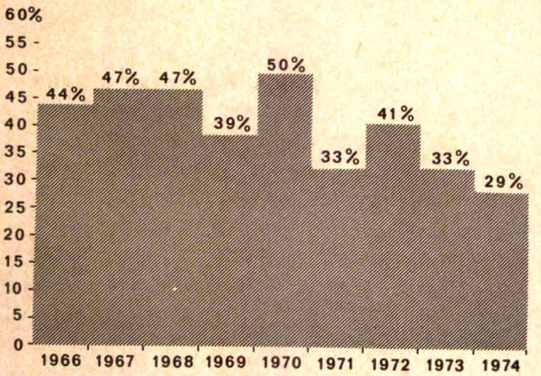

FIGURE 2. Autopsy cases of medically treated congenital heart disease expressed as percent of all autopsy cases of congenital heart disease in each year.

Surgically treated patients ranged from a low of 50 percent of all autopsy cases of congenital heart disease in 1970 to a high of 71 percent in 1974 (average 59 percent from 1966 through 1974, Fig. 3, Table I).

Early versus late deaths: *Early death* (hospital mortality) in 320 cases accounted for 92 percent of 348 postoperative autopsy cases of congenital heart disease from 1966 through 1974. *Late death* (after hospital discharge) in 28 cases accounted for 8 percent of postoperative autopsy cases of congenital heart disease during this 9 year period. The causes of late death in each of these 28 cases are summarized in Table II.

Types of congenital heart disease: The cardiac anomalies associated with early and late postoperative death from 1966 through 1974 are summarized in Table III. For 7 of these 9 years (1970 and 1972 being the exceptions), tetralogy of Fallot, including cases with pulmonary outflow tract atresia and other associated malformations, and *d*-transposition of the great arteries, including cases with additional associated anomalies, were, respectively, the first and second or second and first most frequent types of congenital heart disease associated with postoperative autopsies. During this 9

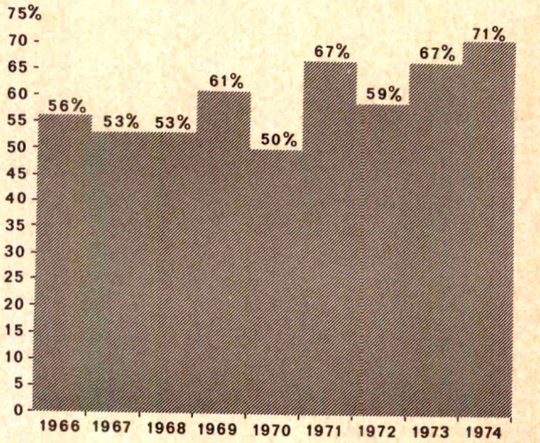

FIGURE 3. Autopsy cases of surgically treated congenital heart disease (CHD) expressed as percent of all autopsy cases of congenital heart disease in each year.

TABLE I

Autopsy Statistics, Children's Hospital Medical Center, Boston, 1966 Through 1974

	1966		1967		1968		1969		1970		1971		1972		1973		1974		Total	
Autopsy Cases	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
All	321		275		295		292		263		280		214		212		213		2,365	
All with CHD*	75	23	58	21	75	25	84	29	60	23	76	27	56	26	54	25	48	23	586	25
Medically treated†	33	44	27	47	35	47	33	39	30	50	25	33	23	41	18	33	14	29	238	41
Surgically treated†	42	56	31	53	40	53	51	61	30	50	51	67	33	59	36	67	34	71	348	59

* Percentages for each year are percentages of all autopsies performed that year.
† Percentages for each year are percentages of all autopsy cases of congenital heart disease that year.
CHD = congenital heart disease.

TABLE II

Late Deaths (by year) in Postoperative Patients (28 cases)

Year	no. (%)	Diagnosis
1966	2 of 42 (5%)	ToF with block, 3 mo postop ToF, shunt occluded by SBE vegetations, 1 1/2 yr postop
1967	5 of 31 (16%)	D-TGA, meningitis 4 1/2 yr post ASD creation D-TGA, aspiration 14 mo post ASD creation Down's syndrome, CCAVC and PS, CHF 2 yr post Potts procedure L-TGA, ⟨S,L,L⟩, VSD and complete A-V block, CHF 1 1/2 mo post pacemaker LCA from PA with EFE of LV, CHF 8 1/2 mo post LCA ligation
1968	0 of 40	
1969	4 of 51 (8%)	ToF with block, 2 2/3 yr postop, pacemaker failure ToF, 2 1/3 yr post repair, recurrent VT Extreme PS with IVS, 3 7/12 yr post Waterston procedure, CHF, PAT ToF, 15 yr post pleural stripping, cyanotic spell
1970	2 of 30 (7%)	P Atr with IVS, 5 3/4 mo post Waterston procedure, arrhythmia Asplenia with PS, 3 mo post Waterston procedure, CHF
1971	5 of 51 (10%)	ToF, 19 yr post Potts, rupture of MPA ToF, 2 1/5 yr post B-T, VF during surgery for spinal fusion ToF, 8 1/3 yr post B-T, sudden unexpected death, ? arrhythmia M Atr with TR, 4 5/6 yr post ASD, massive hemoptysis ToF, 7 3/4 yr post B-T, SBE with massive hemoptysis
1972	1 of 33 (3%)	Subaortic fibrous ring, 1 1/2 mo post repair, fatal hemorrhage from cerebral arteriovenous aneurysm
1973	3 of 36 (8%)	PDA division and MPA band, 3 7/12 yr, aneurysm of pars producing subaortic stenosis "Recoarctation" of aorta, 4 mo postop Asplenia, 5 1/6 yr post Waterston, fulminating pneumococcal septicemia
1974	6 of 34 (18%)	ToF, 6 1/2 yr post repair, recurrent VT → VF D-TGA blocked, 1 mo postop during pacemaker change D-TGA, 11 mo post Rastelli, infected patch from sternal abscess D-TGA, VSD, PS, 22 yr post Potts, rupture of RPA DORV with PS, 4 yr post pleurectomy, brain abscess L-TGA with left-sided T Atr and "subaortic stenosis," 3 1/2 yr post ASD and MPA band, AF then VF

AF = atrial fibrillation; ASD = atrial septal defect; A-V = atrioventricular; B-T = Blalock-Taussig anastomosis; CCAVC = complete common atrioventricular canal; CHF = congestive heart failure; D = dextro; DORV = double outlet right ventricle; EFE = endocardial fibroelastosis; IVS = intact ventricular septum; L = levo; LCA = left coronary artery; LV = left ventricle; M Atr = mitral atresia; MPA = main pulmonary artery; PA = pulmonary artery; PAT = paroxysmal atrial tachycardia; P Atr = pulmonary atresia; PDA = patent ductus arteriosus; postop = postoperatively; PS = pulmonary stenosis; RPA = right pulmonary artery; SBE = subacute bacterial endocarditis; ⟨S,L,L⟩ = situs solitus of the viscera and atria; ventricular *l*-loop and *l*-transposition of great arteries; T Atr = tricuspid atresia; TGA = transposition of great arteries; ToF = tetralogy of Fallot; TR = tricuspid regurgitation; VF = ventricular fibrillation; VSD = ventricular septal defect; VT = ventricular tachycardia.

year period as a whole (Table IV), tetralogy of Fallot was the most common type of congenital heart disease in this series of postoperative autopsies (25.3 percent), and *d*-transposition of the great arteries was second (15.5 percent).

Discussion

Since this is the first presentation of complete and unselected data concerning the postoperative pathologic findings in congenital heart disease, data from other centers are needed to achieve a more complete and representative understanding of this topic.

Congenital heart disease accounted for 25 percent of all autopsies performed at the Children's Hospital Medical Center in Boston during the 9 year study period (Fig. 1, Table I) and was by far the leading cause of death at our hospital during the past decade. Leukemia plus lymphoma was second, constituting approximately 15 percent of all autopsies.[2] Each of the other important causes of death accounted for 10 percent or less of all autopsies. These data are biased by the fact that our hospital is a referral center for major disease in infants and children. Congenital heart disease may also be the leading cause of death in other children's hospitals, but such data are not now available.

Our data show that among the autopsy cases of congenital heart disease, the percent of medical cases is decreasing (Fig. 2) and the percent of surgical cases is increasing (Fig. 3). These statistics are thought to reflect the fact that as our surgical management of congenital heart disease has continued to improve, fewer patients have been managed medically and more have been operated upon. Not only has the percent of our surgical patients increased, but also the progressively more difficult forms of congenital heart disease have been managed surgically in recent years.

In absolute numbers, as opposed to percentages, all autopsy cases are decreasing (Table I). This finding probably reflects the declining birth rate: Fewer autopsies of all kinds are being performed and there are fewer autopsy cases of congenital heart disease, whether medical or surgical, or both.

Types of Congenital Heart Disease

Tetralogy of Fallot, including cases with pulmonary outflow tract atresia and other associated anomalies, was the congenital heart disease most often associated with postoperative death, accounting for 25.3 percent of all postoperative autopsy cases of congenital heart disease (Table IV). *D-transposition of the great arteries,* including cases with additional associated anomalies, was second, constituting 15.5 percent of all postoperative necropsies.

These are unfamiliar statistics. One must be careful not to misread these autopsy statistics as surgical mortality rates. They are not. Instead they are thought to reflect a difficult to dissect mixture of (1) frequency in surgical case load, and (2) surgical difficulty. Initially, we were surprised by these necropsy statistics. We had thought that tetralogy of Fallot was essentially a solved

TABLE III

Malformations Associated with Surgical Death: Early and Late Mortality

Malformation	no. (%)
1966 (42 Cases)	
ToF	11 (26%)
D-TGA	6 (14%)
DORV	5 (12%)
Single ventricle	2 (5%)
Congenital mitral stenosis	2 (5%)
Truncus arteriosus	2 (5%)
P Atr with IVS	2 (5%)
Cardiac malpositions	2 (5%)
VSD	2 (5%)
Ebstein's anomaly	1 (2%)
T Atr	1 (2%)
CCAVC	1 (2%)
Abdominal coarctation	1 (2%)
MR	1 (2%)
AP window	1 (2%)
1967 (31 Cases)	
D-TGA	8 (26%)
ToF	4 (13%)
T Atr	3 (10%)
Single LV	2 (6%)
TAPVC	2 (6%)
ASD I with MR	2 (6%)
Isolated ventricular inversion	2 (6%)
Annulo-aortic ectasia	1 (3%)
Down's syndrome with CCAVC and PS	1 (3%)
Truncus A1	1 (3%)
Ao Atr with IVS	1 (3%)
Aberrant LCA from MPA	1 (3%)
L-TGA	1 (3%)
VSD	1 (3%)
P Atr with IVS	1 (3%)
1968 (40 Cases)	
ToF	14 (35%)
D-TGA	10 (25%)
L-TGA	2 (5%)
P Atr with IVS	2 (5%)
Asplenia	2 (5%)
ASD II	2 (5%)
Preductal coarctation	2 (5%)
PS	1 (2.5%)
Premature closure of FO	1 (2.5%)
Ao Atr	1 (2.5%)
Right ventricular hypoplasia	1 (2.5%)
Rubella syndrome	1 (2.5%)
Polysplenia	1 (2.5%)
ASD II and VSD	1 (2.5%)
1969 (51 Cases)	
ToF	18 (35%)
D-TGA	10 (20%)
P Atr with IVS	3 (6%)
IAA	2 (4%)
Asplenia	2 (4%)
Rubella syndrome	2 (4%)
DORV	2 (4%)
PS (valvular)	2 (4%)
Preductal coarctation	2 (4%)
Ao Atr	1 (2%)
Single LV	1 (2%)
CCAVC	1 (2%)
ASD I with MR	1 (2%)
PDA	1 (2%)
TAPVC	1 (2%)
L-TGA	1 (2%)

Malformation	no. (%)
1970 (30 Cases)*	
ToF	6 (20%)
Preductal coarctation	4 (13%)
TAPVC, supracardiac	3 (10%)
Ao Atr	3 (10%)
Corrected TGA	2 (7%)
Cor triatriatum	1 (3%)
Truncus arteriosus	1 (3%)
VSD	1 (3%)
PS, VSD, AMB	1 (3%)
DORV with PS	1 (3%)
Marfan's syndrome with aortic rupture	1 (3%)
1971 (51 Cases)	
ToF	14 (27%)
TAPVC	5 (10%)
D-TGA	5 (10%)
P Atr with IVS	5 (10%)
PS	2 (4%)
Corrected TGA	2 (4%)
Preductal coarctation	2 (4%)
AS	2 (4%)
M Atr	2 (4%)
ACM IS, D, LI	1 (2%)
Overriding TV	1 (2%)
ASD II, VSD, PDA	1 (2%)
Ebstein's anomaly with PS	1 (2%)
Partial APVC to RA	1 (2%)
Aortic atresia	1 (2%)
Asplenia	1 (2%)
Aberrant LCA	1 (2%)
Ectopia cordis	1 (2%)
Absent PV leaflets	1 (2%)
VSD with MR	1 (2%)
Truncus arteriosus	1 (2%)
1972 (33 Cases)	
P Atr with IVS	6 (18%)
ToF	5 (15%)
D-TGA	2 (6%)
TAPVC	2 (6%)
PDA	2 (6%)
Ao Atr	1 (3%)
DORV	1 (3%)
Corrected TGA	1 (3%)
AS	1 (3%)
Coarctation	1 (3%)
VSD	1 (3%)
DILV	1 (3%)
Subaortic fibrous ring	1 (3%)
VSD with aortic regurgitation	1 (3%)
IAA with AP window	1 (3%)
Isolated levocardia	1 (3%)
ASD I	1 (3%)
Truncus arteriosus with DiGeorge's syndrome	1 (3%)
1973 (36 Cases)	
ToF	9 (25%)
D-TGA	5 (14%)
VSD	3 (8%)
PDA	3 (8%)
TAPVC	2 (5.5%)
Truncus arteriosus	2 (5.5%)
Rhabdomyoma	1 (3%)
Preductal coarctation	1 (3%)
P Atr with IVS	1 (3%)
Asplenia with septicemia	1 (3%)
Polysplenia	1 (3%)

TABLE III (cont'd)

Malformation	no. (%)
1973 (36 Cases) (cont'd)	
CCAVC	1 (3%)
IAA (B)	1 (3%)
T Atr	1 (3%)
AS	1 (3%)
Single LV	1 (3%)
DORV	1 (3%)
1974 (34 Cases)	
D-TGA	8 (24%)
ToF	7 (21%)
VSD	4 (12%)
ASD I	3 (9%)
Preductal coarctation	2 (6%)
IAA	2 (6%)
Truncus arteriosus	1 (3%)
Down's syndrome with CAVC and MPA band	1 (3%)
M Atr with DORV	1 (3%)
DORV, DIRV and PS	1 (3%)
PS, myxomatous	1 (3%)
T Atr with D-TGA	1 (3%)
L-TGA with subaortic stenosis	1 (3%)
{I,S,L,I} atrial noninversion	1 (3%)

* Few Mustard procedures were performed for *d*-transposition of great arteries.

ACM {S,D,L} = anatomically corrected malposition of the great arteries with situs solitus of the viscera and atria, ventricular *d*-loop and *l*-malposition of the great arteries; AMB = anomalous muscle bundles; Ao Atr = aortic atresia; AP = aorticopulmonary; APVC = anomalous pulmonary venous connection; AS = aortic stenosis; ASD I and II = primum and secundum atrial septal defect; DILV = double inlet left ventricle; DIRV = double inlet right ventricle; FO = foramen ovale; IAA = interrupted aortic arch; {I,S,L,I} = situs inversus of the viscera, situs solitus of the atria, ventricular *l*-loop and inverted normal relation between the great arteries, MR = mitral regurgitation; PV = pulmonary valve; RA = right atrium; TAPVC = total anomalous pulmonary venous connection; TV = tricuspid valve. Other abbreviations as in Table II.

surgical problem. However, the data do not support this assumption. Instead, the findings indicate that in terms of the absolute number of postoperative fatalities (as opposed to mortality rates), tetralogy of Fallot is our largest problem, followed by *d*-transposition of the great arteries. Whether this is also true of other diagnostic and therapeutic centers concerned with congenital heart disease is unknown because such information is not now available.

Analysis of the postoperative autopsy statistics by year (Table III) also indicates that tetralogy of Fallot and *d*-transposition of the great arteries were the leading causes of postoperative death from congenital heart disease during this study period. In 7 of the 9 years (1970 and 1972 being the only exceptions), tetralogy and *d*-transposition of the great arteries were, respectively, the first and second or second and first most frequent types of congenital heart disease associated with postoperative autopsy.

Late Mortality

On the basis of available data, the frequency of late postoperative death does not appear to be increasing.

TABLE IV

Malformations Found Most Often in 348 Postoperative Autopsy Cases of Congenital Heart Disease, 1966 Through 1974

	no.	%
Tetralogy of Fallot*	88	25.3
D-transposition of great arteries†	54	15.5

* Including cases with pulmonary outflow tract atresia and other associated malformations.

† Including cases with other associated anomalies.

Table II merits careful scrutiny, each case being a story in itself. Several findings concerning these late postoperative deaths merit specific mention.

Arrhythmias: Arrhythmias were important: tetralogy with A-V block (1966); tetralogy with A-V block and tetralogy with recurrent ventricular tachycardia (1969); pulmonary atresia with intact ventricular septum, presumed ventricular tachyarrhythmia (1970); tetralogy of Fallot after a Blalock-Taussig anastomosis, with ventricular fibrillation during operation for spinal fusion, presumably as a result of intraoperative hypotension (1971); and tetralogy of Fallot with recurrent ventricular tachycardia progressing to ventricular fibrillation (1974).

In two cases, excessive right ventricular myocardial resection in tetralogy of Fallot was associated with recurrent ventricular tachyarrhythmias 2 and 6 1/2 years postoperatively (1969, 1974).

In patients with pulmonary atresia and intact ventricular septum supraventricular tachyarrhythmias and congestive heart failure developed apparently because of right atrial enlargement (1969, 1970). The possibility of a ventricular component in fatal arrhythmias in this disease must also be borne in mind, in view of the possibility of coronary arterial abnormalities (thick walls, small lumens, interruptions), sinusoids and the often striking myocardial bypass as right ventricular blood passes into the coronary arteries by way of sinusoids, followed by retrograde coronary blood flow.

Obstructively small ventricular septal defect: In one case this developed in association with tricuspid atresia (left-sided). Since the patient also had *l*-transposition of the great arteries {S,L,L}, the obstructively small ventricular septal defect resulted in an unusual form of muscular "subaortic stenosis" (1974). It may be possible to enlarge such a ventricular septal defect surgically along its margin inferiorly, but probably not superiorly because of the conduction system in *l*-loops, thereby relieving the muscular subaortic stenosis. Intraoperative mapping of the conduction system should make it possible to avoid block.

Other causes of late death: Massive hemoptysis leading to late postoperative death in two cases was associated with subacute bacterial endocarditis (1971) and with pulmonary hypertension (1971). Rupture of a pulmonary artery occurred without known bacterial endocarditis in two cases approximately 20 years after

the creation of a Potts anastomosis (1971, 1974). A fatal cyanotic spell occurred in a patient with tetralogy of Fallot 15 years after pleural stripping (1969). Congestive heart failure led to late postoperative death in three cases in association with an excessively large Waterston or Potts anastomosis (1967, 1969, 1970).

Infection: Infection was important: occlusion of a shunt in tetralogy of Fallot by vegetations of subacute bacterial endocarditis (1966); meningitis in surgically palliated *d*-transposition (1967); subacute bacterial endocarditis in tetralogy resulting in massive hemoptysis (1971); sternal abscess leading to infection of Rastelli conduit in *d*-transposition (1974); brain abscess in double outlet right ventricle with ventricular septal defect and pulmonary stenosis (1974); and fulminating pneumococcal septicemia in a 5 year old boy with asplenia (1973).

Penicillin prophylaxis for the asplenia syndrome: The aforementioned 5 year old boy died less than 24 hours after the onset of a fulminating febrile illness that proved to be a pneumococcal septicemia. It is now known that the spleen performs an important role in the preliminary opsonization of encapsulated bacteria such as the pneumococcus with specific antibodies in order to facilitate their phagocytosis.[3] This case, plus the new understanding of the immunologic role of the spleen in the body's defenses against the pneumococcus, strongly suggested that one should give serious consideration to the possibility of providing prophylactic penicillin to patients with the asplenia syndrome, similar to that given to patients with a history of rheumatic fever. If one decides against such prophylaxis, then it would at least seem wise to give such patients large doses of penicillin at the first indication of a flu-like, febrile illness. However, the fulminating time course of the pneumococcal septicemia in our patient was so rapid and devastating, with profound leukopenia, that we now recommend penicillin prophylaxis for survivors of the asplenia syndrome with successful palliation.

Future Projections

Our findings strongly suggest that the major problem of the postoperative patient with congenital heart disease, as seen from the standpoint of cardiac pathology, will continue to be hospital mortality (92 percent of our postoperative series) rather than late mortality (8 percent). However, the need for careful, long-term postoperative follow-up of patients with congenital heart disease is apparent, since many questions can be answered satisfactorily only in this way.

In view of the relative consistency of the findings over the years, namely, that tetralogy of Fallot and *d*-transposition of the great arteries were the leading causes of death from congenital heart disease during 7 of the 9 years of this study period, it seems probable that in the near future, tetralogy of Fallot (including cases with pulmonary outflow tract atresia and other associated malformations) and *d*-transposition of the great arteries (including cases with other associated anomalies) will continue to be leading causes of postoperative death from congenital heart disease in terms of the absolute number of fatalities (as opposed to percent of fatalities). Efforts to improve the management of patients with tetralogy of Fallot and with *d*-transposition of the great arteries are clearly warranted.

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Addendum

After completion of this paper, a study by Waldman et al.[4] confirmed that the frequency of fulminating fatal septicemia with encapsulated bacteria is much greater in patients with congenital asplenia than in appropriate control subjects: Klebsiella and Escherichia coli before age 6 months, and pneumococcus and Haemophilus influenzae from age 6 months onward. Consequently, Waldman et al.[4] recommend continuous antibiotic prophylaxis in children and adults with congenital asplenia: amoxicillin (25 mg/kg per day in two divided doses, maximum 1 g/day) or ampicillin (50 mg/kg per day in four divided doses, maximum 2 g/day).

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Long-Term Follow-Up of Valvulotomy for Congenital Aortic Stenosis

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The data were reviewed of 42 patients who had valvulotomy for severe aortic valve stenosis before 1968. All were over age 2 years (mean age 11.3 years). The mean time of follow-up after surgery was 10.6 years (range 6 to 16.3 years). No patient died at operation. Two late deaths were from endocarditis with aortic regurgitation, and one patient with severe aortic regurgitation died suddenly; three patients had valve replacement for aortic regurgitation and one required repeat valvulotomy. Five patients could not be traced.

Major symptoms were alleviated in all patients. Left ventricular pressures were obtained in 15 patients before and after operation; the mean gradient averaged 100 mm Hg before and 43 mm Hg after operation. No patient had significant aortic regurgitation before operation. Twelve had moderate to severe regurgitation after operation. The incidence of late valve calcification at a mean time of 10.6 years after operation was small, and restenosis was uncommon. Because moderate or severe incompetence can be produced and stenosis is often incompletely relieved, the operation is palliative, but the low morbidity and mortality rates suggest that it is an effective procedure if stenosis is severe and life-threatening.

In the past 2 decades aortic valve commissurotomy has usually been recommended for children and young adults with severe congenital aortic valve stenosis. Stenosis has been adequately relieved in most patients and operative morbidity and mortality rate have been low.[1–3] The early and later results of surgery have been favorable,[3–7] further suggesting that this is the correct management for severe aortic stenosis.

Although patients with congenital aortic stenosis who have had valvulotomy are told they will eventually require valve replacement, the long-term fate of most of these patients is uncertain. This study is an attempt to determine the long-term results of aortic valvulotomy in 42 patients with congenital aortic stenosis who were operated on between 1956 and 1968 at the Johns Hopkins Hospital. The data in some of these cases were reviewed in an earlier report.[1]

Method

Forty-two patients over 2 years of age who had aortic valvulotomy for congenital aortic stenosis were reviewed. Cardiac symptoms, physical signs, electrocardiographic and chest X-ray findings were evaluated retrospectively before operation, 1 year postoperatively and in 1974 (mean time 10.6 years postoperatively; range 6 to 16.3 years). Patients were initially operated on for cardiac symptoms, electrocardiographic changes consistent with left ventricular hypertrophy or strain, or a peak systolic gradient greater than 60 mm Hg at cardiac catheterization. Six patients were asymptomatic before operation, 25 had easy fatigability and mild dyspnea, 3 had angina pectoris, 6 had episodes of syncope, 1 had dizziness and 1 had nocturnal dyspnea.

Left ventricular pressure was measured in 15 patients before operation and in 20 patients after operation. The findings are presented in Table I.

Surgical technique: Between 1957 and 1968 surgery was performed using cardiopulmonary bypass, initially with potassium-induced cardiac arrest, later

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TABLE I
Hemodynamic Data

Case no.	Aortic Valve Peak Systolic Gradient (mm Hg)		Years After Surgery	Aortic Regurgitation
	Preop	Postop		
1	106	65	4.0	Mild
2*	92	120	4.8	Mild
3*	120	12	1.8	Mild
4	209	57	10.3	Mod
5	116	78	6.7	Mod
6	. . .	24	7.1	Mod
7	. . .	21	14.1	Mod—severe
8	70	16	4.0	Mod
9	. . .	18	14.8	Nil
10	100	40	1.2	Mild
11	. . .	93	12.2	Mod—severe
12	110	70	2.8	Mod
13	. . .	25	15.1	Mod
14	105	11	9.0	Mild
15	83	11	4.1	Mod
16	89	0	4.1	Severe
17	100	64	7.8	Mod
18	93	10	6.9	Mod—severe
19	102	28	8.7	Mild
20	65	47	11.5	Mild
Mean	104	43	. . .	. . .

*Same patient with successive valvulotomies.
Postop = postoperative; preop = preoperative.

with intermittent coronary arterial perfusion during aortic cross-clamping and, more recently, with hypothermia. The technique used was that of open valvulotomy from the aortic root.[1] The usual anatomic abnormality found at operation was a bicuspid aortic valve. Associated cardiovascular anomalies included coarctation of the aorta (one patient) and patent ductus arteriosus (one patient). The former was repaired 6 months after aortic valvulotomy, the latter at the time of valvulotomy.

Results

Immediate Postoperative Period

All 42 patients survived the operation. The mean age at operation was 11.3 years (range 3 to 28 years). Complications were uncommon and minor. Aortic regurgitation was noted in four patients before operation. Clinical findings at the time of discharge were available in 26 patients, and 21 had an early diastolic murmur suggesting aortic regurgitation.

One Year Postoperative Follow-Up

Five patients were entirely asymptomatic before operation and remained so postoperatively. Eleven patients who had a major symptom such as nocturnal dyspnea, dizziness, syncope or angina pectoris before operation were asymptomatic 1 year after operation. Of 25 patients who admitted to mild symptoms of fatigability or mild dyspnea, 24 were asymptomatic 1 year later. Thirty-five patients had aortic regurgitation; in 12 it was assessed on clinical examination as moderate or severe. The other physical signs were difficult to evaluate retrospectively but the typical murmur of congenital aortic stenosis was present in all.

Electrocardiographic evidence of left ventricular hypertrophy: The electrocardiograms were compared before and 1 year after operation in 40 patients. Left ventricular hypertrophy was diagnosed on the basis of voltage criteria when the S wave in lead V_2 plus the R wave in lead V_5 was greater than 45 mm. A left ventricular strain pattern was noted when symmetrical T wave inversion was present in the inferior or lateral chest leads.

Before operation 9 patients had no evidence of left ventricular hypertrophy; 11 had left ventricular hypertrophy with voltage criteria; 20 had a pattern of left ventricular hypertrophy with strain.

Postoperatively, the abnormal inverted T waves returned to normal in 14 of the 20 patients with a strain pattern; 6 patients showed no improvement (4 with moderate to severe aortic regurgitation postoperatively and 2 with severe residual stenosis).

Of 11 patients with left ventricular hypertrophy on the basis of voltage criteria, 3 had normal findings postoperatively; 3, all with moderate aortic regurgitation, had a more severe pattern of left ventricular hypertrophy with strain, and in 5 the pattern was unchanged. In two of the nine patients with a normal electrocardiogram before operation, left ventricular hypertrophy developed postoperatively; both patients had moderate aortic regurgitation clinically. The failure of resolution or appearance of a pattern of left ventricular hypertrophy or strain 1 year postoperatively was associated with moderate or severe aortic regurgitation produced at operation (three cases) or with residual stenosis (two cases).

One patient had a P-R interval of 0.2 second; the QRS duration was normal in all before and after operation. One patient had left axis deviation, one had right axis deviation, the rest had a normal axis. No arrhythmias were noted.

The cardiothoracic ratio in the posteroanterior chest roentgenogram was assessed in 28 patients preoperatively and was normal; there was no significant change after operation.

Long-Term Follow-Up

Of the original 42 patients, 37 were assessed at a recent followup; the data in 5 who could not be contacted were excluded from the analysis. The mean time after operation was 10.6 years (range 6 to 16.3 years). Three patients had died. One who had severe aortic regurgitation died suddenly 4.4 years after operation and the other two died of infective endocarditis 3.3 and 6.3 years, respectively, after operation. Three patients who experienced exertional dyspnea and cardiac enlargement from severe aortic incompetence required aortic valve replacement 5.3, 10.3 and 14.2 years, respectively, after operation. All three patients survived and were asymptomatic when last seen. A further patient had repeat valvulotomy for aortic stenosis. Although some restenosis was thought to have occurred, the original operation was probably inadequate; a satisfactory reduction in stenosis was achieved at the second valvulotomy.

Clinical findings: The remaining 31 patients were evaluated clinically with posteroanterior and lateral chest roentgenograms and, when available, electrocardiograms. The mean time after operation was 12.2 years (range 6 to 16.3 years). Twenty-one patients were thought to have mild residual disease and were

asymptomatic. Ten patients clinically had the physical signs of severe aortic stenosis or incompetence with cardiomegaly. All had a pattern of severe left ventricular hypertrophy with strain in the electrocardiogram. Those with clinically significant valve incompetence had cardiomegaly. Further surgery was recommended for all 10 patients.

The presence of calcium in the aortic valve was assessed with fluoroscopy in 15 patients and with the lateral chest X-ray film in the remaining patients. Only one patient had a calcified valve.

Hemodynamic Assessment

Seventeen patients had left-sided pressure measurements before operation. Many of these patients were assessed before left heart catheterization had become a routine procedure in this institution. In some, left ventricular pressure was obtained by transthoracic left ventricular needle puncture; aortography was performed in only three patients preoperatively.

Postoperative cardiac catheterization: Twenty patients had postoperative cardiac catheterization electively and not because of development of symptoms. In 15 patients pre- and postoperative pressure data could be compared. The mean time after operation in these patients was 5.8 years, and the mean aortic valve gradient was 104 mm Hg preoperatively and 43 mm Hg postoperatively ($P < 0.001$) (Fig. 1). One patient with a postoperative gradient of 120 mm Hg had a further valvulotomy 6.8 years after the first, and the gradient was reduced to 12 mm Hg. This was the only patient who had repeat valvulotomy.

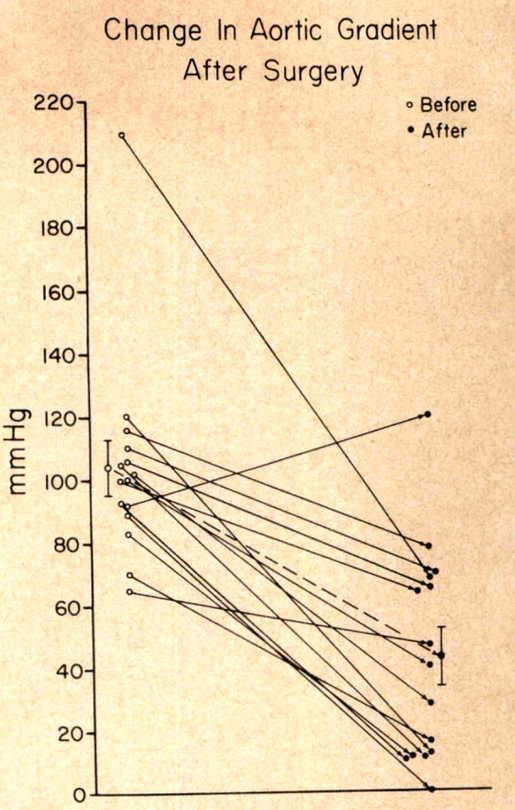

FIGURE 1. The peak systolic gradients between the left ventricle and aorta (**open circles**) before and after (**closed circles**) operation. The **dotted line** represents the mean and the **vertical bars** 1 standard error of the mean.

Discussion

The criteria for operation in congenital aortic stenosis have changed little over the years. Patients with a peak systolic gradient of 60 mm Hg or greater are recommended for surgery[8] unless unusual anatomic features such as a unicuspid valve are present.[9] The patients are typically children or young adults and few have major symptoms of angina, syncope or heart failure, but the risk of sudden death even in asymptomatic patients plus the myocardial damage associated with long-standing left ventricular hypertrophy are the accepted reasons for operation in patients without symptoms or in those with only fatigue or mild dyspnea of effort. The published reports of the results of surgery in congenital aortic stenosis are often difficult to analyze, and discrete left ventricular outflow obstruction at subvalvular or supravalvular levels is often included in series of patients with obstruction at the valvular level.[1,3,4,5] Because these conditions require different operative techniques, results of a pooled analysis of postoperative progress may be confusing.

Children less than 2 years old who had surgery for aortic valve stenosis were not included in our series because infantile aortic stenosis is usually a complex entity often associated with underdevelopment of the left heart chambers and high medical and surgical mortality rates.[10]

Valve calcification: The natural history of aortic valve stenosis reveals that the frequency of valve calcification in childhood and adolescence is low but increases with age.[5,11] There are no data in this study to suggest that valve calcification is either lessened or developed by prior valvulotomy. Only one patient was found to have a calcified valve at follow-up study, and he was aged 39 years, the oldest patient in the series. At operation 11.5 years earlier, no calcium was noted in the valve.

Restenosis or residual stenosis: Restenosis appears to occur infrequently.[12] In our series objective hemodynamic findings were available in only 20 patients postoperatively and at only one point in time, and restenosis was difficult to assess. In one patient (Case 2) reoperation decreased the gradient from 120 mm Hg to 12 mm Hg and the residual gradient may have been due to inadequate initial surgery rather than restenosis. Many patients thought to have restenosis probably have had inadequate valvulotomy; this observation emphasizes the value of performing cardiac catheterization studies within a year after operation so that an objective measurement of residual stenosis may be made because the clinical assessment alone is often unreliable. Calcification undoubtedly would cause restenosis, but we have shown this to be uncommon even after operation in the younger age groups. After age 35 years, patients should be carefully assessed with fluoroscopy to determine if calcium is present in the valve since its presence may indicate significant restenosis.[5,11]

Residual stenosis was significant in this series. Of the 15 patients who had gradients measured before and after operation, 6 had a significant residual gradient of more than 60 mm Hg. This degree of obstruction is an indication for surgery in patients not previously treated surgically for aortic valve stenosis.[8] As mentioned, reoperation in our Case 2 resulted in a reduction of the gradient from 120 to 12 mm Hg. In the remaining five patients, the degree of stenosis was significantly reduced from the preoperative level. Repeat valvulotomy was not considered because of the anatomic features observed at the time of operation, and prosthetic valve replacement was not believed to be justified at that time.

Aortic regurgitation: The major complication of aortic valvulotomy is aortic regurgitation.[5,6] The murmur of aortic regurgitation was noted in 10 percent of our patients before operation and in 80 percent after operation. In 25 percent of all postoperative patients, the aortic regurgitation was thought to be moderate or severe. One patient with severe regurgitation died suddenly; three required valve replacement, and a further three were awaiting valve replacement at the time of review. This series deals with patients who were operated on 6 to 16 years ago. Improved preoperative assessment of the valve and greater awareness of the potential hazard of aortic regurgitation have probably decreased the incidence of this complication over the years.

Endocarditis: Two patients died of infective endocarditis and both had significant aortic regurgitation. The danger of endocarditis is always present in patients with aortic valve disease and is not related to its severity. A greater awareness of this serious complication and careful prophylaxis during dental procedures and surgery may decrease the incidence.

Criteria for reoperation: The criteria for reoperation in patients who have previously had aortic valvulotomy is difficult to define. One third of our patients had no major symptoms but were recommended for valve replacement because of significant residual stenosis at cardiac catheterization or moderate to severe valve incompetence clinically, evidence of severe left ventricular hypertrophy in the electrocardiogram and cardiomegaly in the chest roentgenogram. This large percentage of patients, all of whom have been regularly followed up medically, illustrates the difficult problem the younger person with a previous aortic valvulotomy presents to the cardiologist. Because of the danger of sudden death or irreversible myocardial damage and the good results of valve replacement we now recommend that reoperation in these patients not be deferred too long. In patients who have previously had aortic valvulotomy the degree of residual stenosis is often difficult to estimate clinically and all patients should be recatheterized within 1 year after operation and approximately every 5 years thereafter unless earlier study is prompted by clinical events.[4] The failure of resolution of a preoperative pattern of left ventricular hypertrophy in the electrocardiogram should also suggest the presence of significant aortic valve disease.

Clinical implication: Our findings suggest that aortic valvulotomy should continue to be performed in preference to aortic valve replacement in children and young adults. The incidence rate of restenosis is low, and calcification causing further obstruction does not seem to occur until the 4th decade. Significant residual stenosis is common and moderate to severe aortic regurgitation is frequently produced. After operation the quality of life is good, and the annual mortality rate was only 0.5 percent in this series. This compares favorably with other reported annual mortality rates of 1.1 to 1.7 percent in medical and surgical series of young patients with aortic stenosis.[12,13] The operative mortality rate of prosthetic valve replacement is low (about 5 percent),[14,15] and the incidence of complications such as embolism has decreased, but the difficulty of insertion of a valve in a small child and the long life expectancy preclude valve replacement as the definitive operation for congenital aortic valve stenosis in children.

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Tricuspid Atresia: Results of Treatment in 160 Children

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Experience in managing 160 patients with tricuspid atresia is reviewed. The majority of these children require operative treatment in the 1st year of life. Clinical management of this rather complex anomaly is simplified by classifying each child according to total pulmonary blood flow. An overall plan of management for patients with decreased pulmonary flow is suggested. This consists of a Potts shunt as an initial procedure, limiting its anastomotic growth so that pulmonary flow becomes inadequate at age 10 to 12 years. A Glenn anastomosis is then constructed as the second procedure. The Fontan procedure should be considered carefully as an alternative to the Glenn anastomosis in these older children.

Children with increased pulmonary blood flow and transposition of the great arteries are likely to require pulmonary arterial banding in infancy. Otherwise, patients in this smaller group are managed with the same overall plan. Results of long-term palliation have been good.

The introduction by Fontan and Baudet[1] of a physiologic repair for tricuspid atresia led us to review our experience in managing this uncommon form of congenital heart disease. Tricuspid atresia is a spectrum of malformations with four features in common, namely, atresia of the right atrioventricular (A-V) valve, interatrial communication, hypertrophy of the left ventricle and hypoplasia or absence of the right ventricular sinus. Variation in pulmonary outflow tract obstruction and the relation of the great vessels produces a wide variety of clinical findings.[2]

Most infants with the tricuspid atresia complex need surgical intervention early in life. We have assessed our present palliative methods as to operative risk and long-term prognosis in the hope of using this information as a background to determine the timing of physiologic repair as proposed by Fontan and Baudet.

General Data

One hundred sixty patients with tricuspid atresia were seen at the Hospital for Sick Children between 1947 and July 1974. Analysis of the records of these patients forms the basis of this report.

Classification of the types of tricuspid atresia according to the criteria of Keith et al.[3] is shown in Table I. Associated anomalies were not common in this group of patients; right aortic arch was present in only eight patients (5 percent) and bilateral superior vena cava in nine (5 percent). Clinical management is facilitated by a much simpler classification according to estimated total pulmonary blood flow. Eighty-five percent of our patients presented with decreased and 15 percent with increased pulmonary flow (Table II).

Sex distribution was approximately equal; there were 76 male and 84 female patients. The follow-up period ranged from 6 months to 22 years. *The overall results are illustrated in Table III.*

Details of management will be discussed according to the clinical classification of pulmonary blood flow at the initial examination.

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Management and Results

Group A: Decreased Pulmonary Blood Flow

One hundred thirty-six children (85 percent of the series) presented with decreased pulmonary blood flow. Cyanosis was obvious in the 1st month of life in 92 percent of these infants. The subgroup of 21 patients with pulmonary atresia presented for treatment earlier in life and were in more critical condition than those with pulmonary stenosis (115 patients); all 21 were hospitalized by age 6 months.

Palliation of these infants begins with the diagnosis at cardiac catheterization. Balloon atrial septostomy is performed to permit nonobstructed blood flow from the right to the left atrium.[4] This procedure has been carried out in all infants since 1966. Only eight infants in the entire series underwent operative atrial septectomy, and each of these patients had a shunt performed at the same time.

Surgical intervention to augment pulmonary blood flow is advised when the child has cyanotic spells, severe hypoxia or acidosis. Twenty-three percent of our patients with decreased pulmonary blood flow were operated on in the 1st month of life, 66 percent during the 1st year of life.

Early Results

Nonsurgical cases: Of the 136 children with decreased pulmonary blood flow, 27 had no operative procedures. Twenty-one of these infants died before age 6 months and five more died before age 2 years. One child is currently surviving with adequate pulmonary flow at age 16 months. This small group does not represent the natural history or results of "medical" treatment of tricuspid atresia. Most of these patients were seen early in our experience, and the need for surgical intervention was often not recognized. In some cases, the diagnosis was not made until postmortem examination. However, this experience does suggest the lethal nature of the tricuspid atresia complex in the infant.

Surgical results: The remaining 109 children with decreased pulmonary blood flow underwent operation. The operative and hospital mortality was inversely related to age (Tables IV and V). The very high risk group

TABLE I

Anatomic Classification of Tricuspid Atresia

	Relation of Great Vessels		
	Group I (Normal Relation)	Group II (D–TGV)	Group III (L–TGV)
A (pulmonary atresia)	21	3	Subpulmonary stenosis 3
B (pulmonary stenosis)	93	16	Subaortic stenosis 0
C (no pulmonary stenosis)	14	10	. . .

D–TGV = dextrotransposition of the great arteries; L–TGV = levotransposition of the great arteries.

TABLE II

Clinical Classification of Tricuspid Atresia

	Patients	
	(no.)	%
Group A (decreased pulmonary blood flow)		
1. Pulmonary stenosis	115	
2. Pulmonary atresia	21	
Total	136	85
Group B (increased pulmonary blood flow)	24	15

TABLE III

Tricuspid Atresia: Overall Results in 160 Patients to July 1974

	Patients	
	no.	%
Current survivors		
>20 years old	5	
10-20 years old	37	
<10 years old	28	
Total	70	44
Mortality*		
Nonoperative	32	
Operative (in hospital)	44	
Late	11	
Total	87	54
Lost to follow-up	3	2

*Of the 87 deaths, 76 percent occurred in infants less than 1 year of age.

TABLE IV

Tricuspid Atresia: Hospital Mortality with Decreased Pulmonary Blood Flow

Procedure	Patients <6 Months Old	Patients >6 Months Old
Potts	13 of 30 (43%)	3 of 19 (16%)
Blalock-Taussig	7 of 14 (50%)	3 of 30 (10%)
Glenn	2 of 4	1 of 26 (4%)
Waterston	2 of 6	1 of 3
Miscellaneous	6 of 7	1 of 6
Total	30 of 61 (50%)	9 of 84 (11%)

TABLE V

Mortality in Patients With Arterial-Pulmonary Shunt

Age Group	Patients (no.)	Mortality Rate (%)
<1 week	11	60
1 week to 1 month	14	50
1 month to 6 months	32	44
>6 months	52	13

is less than 6 months old. One fourth of those undergoing palliative shunts were under age 1 month, and almost half of this group were in the 1st week of life. Recently there has been some reduction of mortality in the infant group, but our operative mortality rate for Potts shunt in infants less than 6 months of age has been 33 percent (5 of 15) over the past 9 years.

In children older than 6 months, the operative mortality rate is much lower (for example, 13 percent for patients with an arteriopulmonary shunt and 4 percent for those with a cava-pulmonary anastomosis). Although these results may suggest that operation should be deferred until after age 6 months, this was not possible in at least half of our patients who required shunting on an urgent basis.

Late Results

Late deaths: Seventy patients who had shunts to augment pulmonary blood flow were discharged from the hospital after operation and have been followed up for 6 months to 22 years (mean follow-up period 9.6 years).

There have been 11 late deaths in these 70 patients. One patient died at reoperation for increasing cyanosis 10 years after the initial Potts shunt; one died of an unrelated cause (Ewing's sarcoma); four died of related causes (sepsis, pulmonary infarct [two patients] and pulmonary hypertension); and five other patients died of unknown causes. The single late death from pulmonary hypertension occurred 18 years after operation in a patient without transposition of the great arteries who underwent a Blalock-Taussig shunt at age 18 months. Pulmonary vascular disease has not been a late clinical problem although a definitive statement is not possible without hemodynamic follow-up studies.

Repeat shunt procedure: Thirty-eight patients (38 of 70) with a single shunt procedure are currently surviving an average of 9.6 years postoperatively (range 6 months to 22 years). Twenty-one patients have required an additional shunt procedure an average of 6 years (1.5 to 10.5 years) postoperatively (Table VI). Four of these patients have required more than two shunts for palliation. The mortality rate of those reoperated on has been low.

Comparison of three shunt procedures: Figures 1 and 2 compare the effective palliation of the three

TABLE VI

Tricuspid Atresia: Reoperation for Decreased Pulmonary Blood Flow in 21 Patients*

Reoperative Procedure	no.
Glenn	10
Potts	9
Blalock	7
Waterston	2
Miscellaneous	3
Total	31

*There was 1 death in the 31 procedures (mortality rate of reoperation 3.1 percent).

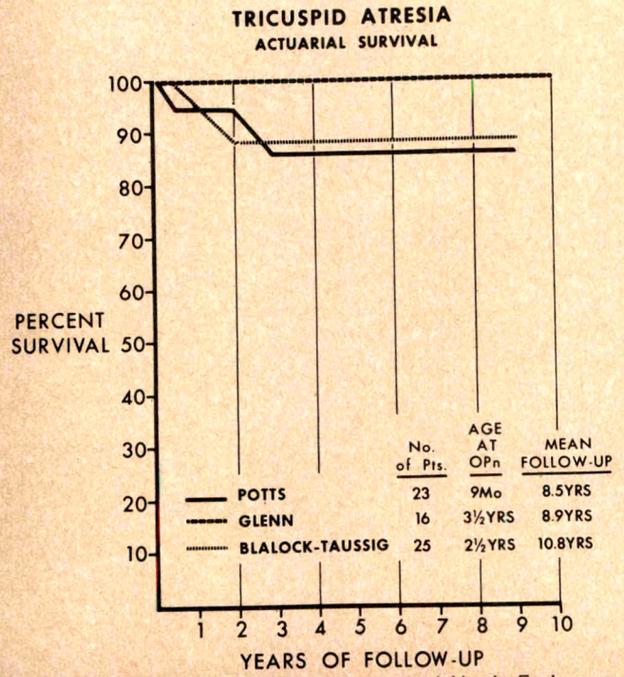

FIGURE 1. Patient survival charted on an actuarial basis. Each group of patients has survived a single shunt procedure. Seven years after operation, 90.7 percent of these patients are alive; 25 percent are asymptomatic and 65 percent have mild limitation of exercise tolerance. There are no late deaths in the group with a Glenn shunt (16 patients followed up an average of 8.9 years). OPn = operation; Pts = patients.

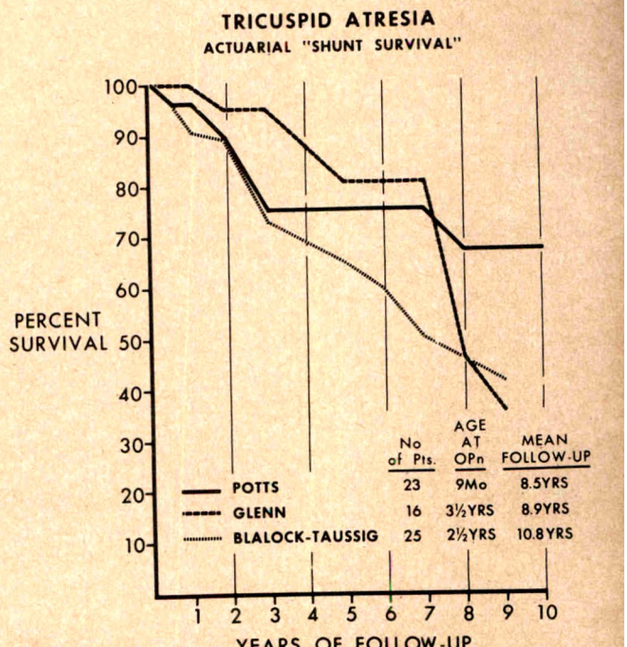

FIGURE 2. "Shunt survival" indicated by the time that each group of patients survives before requiring a second shunt. Seven years postoperatively, 75 percent of the patients who underwent a Potts shunt as their initial procedure are still being maintained adequately compared with 81 percent of the patients with a Glenn anastomosis and only 50 percent of those with a Blalock-Taussig shunt. Abbreviations as in Figure 1.

major shunts used. Figure 1 demonstrates *patient survival* calculated by the actuarial method for three groups of patients who survived either a Potts shunt, a Glenn anastomosis or a Blalock-Taussig shunt as an initial procedure. No deaths have occurred in the follow-up period in the 17 patients whose initial operation was a Glenn shunt. This was an ideal group to treat because they had survived the high risk of early infancy and came to operation at a mean age of 3.5 years. Long-term survival rates of the other two groups are not statistically different in spite of the younger age at operation in patients with a Potts shunt.

Figure 2 illustrates the period of time during which the initial shunt functions adequately to maintain the patient in reasonable health. The actuarial method has been used to calculate the period of adequate shunt function. Death of the patient, occlusion of the shunt or reoperation in spite of a functioning shunt have all been counted as shunt failure. Seven years after initial operation, 75 percent of the patients with a Potts shunt are still being maintained adequately compared with 81 percent of patients with a Glenn shunt and only 50 percent of those with a Blalock-Taussig shunt.

Functional status: At the time of follow-up, 25 percent of the survivors were asymptomatic and 65 percent mildly symptomatic although able to walk 6 blocks and engage in mild sports activity. Ten percent were severely restricted, becoming dyspneic with minor exertion. In two children brain abscesses developed during the follow-up period.

Group B: Increased Pulmonary Blood Flow

Only 15 percent (24 patients) of the children with the tricuspid atresia complex presented with clinical evidence of increased pulmonary blood flow. Despite the increased flow, 50 percent of these patients were cyanotic at birth and all eventually became cyanotic. Congestive heart failure was a particularly common presenting symptom in patients with transposition of the great arteries, nine of whom were hospitalized for congestive heart failure in the 1st 3 months of life. Conversely, infants with normally related great vessels usually presented with cyanosis (10 of 14 patients) somewhat later in life (mean age 9 months) (Table VII).

Surgical results: Pulmonary arterial banding was carried out in six infants to control intractable congestive heart failure (Table VIII). Five of these infants had transposition of the great arteries. The mean age at operation was 3 months (range 6 weeks to 5 1/2 years). There were two operative deaths and two of the four survivors have had a subsequent shunt (Glenn operation 3 and 10 years, respectively, after banding) with good results. The four survivors are now aged 3 1/2 to 10 1/2 years (mean 6 years).

Palliative shunting was necessary in five children when cyanosis became progressive (Table VIII). All of these children had normally related great arteries, a left aortic arch and pulmonary stenosis. The age at operation averaged 2 years 9 months (range 5 months to 4 years). One of these children died at operation, the other four are doing well and are now aged 1 1/2 to 16 years (mean 8 years).

In one patient total repair was attempted in 1957 but was unsuccessful.

Nonsurgical patients: Ten patients with increased pulmonary blood flow have been followed up without operation. Six of these children have died, four of congestive heart failure before age 3 months (three with transposition of the great arteries) and two of hypoxia at age 9 and 10 months, respectively. Of the four survivors, two are well at the respective ages of 7 1/2 and 9 1/2 years. One patient with transposition of the great arteries has severe pulmonary vascular disease at age 14 years and one has been lost to further follow-up.

Discussion

Without treatment two thirds of infants born with tricuspid atresia die before their 1st birthday.[3] This natural history justifies an aggressive surgical approach.

Palliative shunts for decreased pulmonary blood flow: Eighty-five percent of our 160 patients with tricuspid atresia presented with signs and symptoms of decreased pulmonary blood flow. Most of these (66 percent) required surgical palliation in the 1st year of life. Selection of the operation to augment pulmonary blood flow depends upon the child's age. In infants less than 6 months of age we have elected to use a Potts shunt. The mortality rate has been high in this age group regardless of the type of operation. In the infants, the Potts descending aorta to pulmonary artery anastomosis offers a higher rate of technical success than a

TABLE VII

Tricuspid Atresia: Presenting Symptoms With Increased Pulmonary Blood Flow

Relation of Great Vessels	CHF	Cyanosis	Total
Normal	4	10*	14
Transposed	9†	1	10
Total	13	11	24

*Mean age 9 months.
†Mean age 3 months.
CHF = congestive heart failure.

TABLE VIII

Tricuspid Atresia With Increased Pulmonary Blood Flow: Surgical Procedures

	Total Patients	Survivors	Current Age (yr)
Pulmonary arterial banding (mean age 3 mo)	6	4*	3 1/2–10 1/2
Palliative shunt (mean age 2 3/4 yr)	5	4	1 1/2–16
Coarctectomy	2	0	
No operation	10	4	
Total	23	12	

*Two of the four patients had a subsequent Glenn operation.

subclavian artery to pulmonary artery shunt. Our results suggest that the Potts shunt also has a better long-term prognosis (Fig. 1). We have found it easier to construct and more predictable than a Waterston (ascending aorta to right pulmonary artery) shunt. In children more than 2 years of age, we have used a superior vena cava to pulmonary artery shunt (Glenn anastomosis). The operative mortality rate has been low (4 percent) and there has been no late mortality. Long-term improvement is excellent for at least the first 6 years postoperatively. Clinical deterioration appeared to occur in our patients 6 to 8 years postoperatively (Table I), and has been observed by others.[5,6] We believe that it is due to the child's outgrowing his total pulmonary blood flow in spite of a functioning and growing cava-pulmonary anastomosis. In our series, the Blalock-Taussig shunt has been used primarily for children requiring operation between 6 months and 2 years of age. The operative risk has been 10 percent in these patients, and the long-term results have been less satisfactory than those of the Potts or Glenn shunt. For example, the probability of a child being maintained adequately by his initial procedure 7 years postoperatively is 75 percent with a Potts, 81 percent with a Glenn and 50 percent with a Blalock-Taussig shunt.

Repeated or combined shunts: As it has evolved, our overall plan in the patients with tricuspid atresia has been to construct an aortopulmonary shunt initially and to preserve the side of the chest with the superior vena cava for a later Glenn anastomosis. Five percent of our patients have had bilateral superior vena cava and in this group an attempt has been made to ligate the smaller vena cava at the time of a systemic pulmonary arterial shunt. We do not have sufficient long-term data to analyze the results of combined surgical procedures. In the 21 patients reoperated on to date, there has been 1 death in 31 procedures (3.2 percent mortality rate). It seems likely that the benefit from combining the procedures will be at least additive, in which case, the infant surviving a Potts shunt and subsequently a Glenn shunt should have adequate palliation to early adulthood.

Surgical palliation for increased pulmonary blood flow: Relatively few patients (15 percent) with tricuspid atresia present with increased pulmonary blood flow. Forty-two percent (10 of 24) of the patients in our series with increased flow had transposition of the great arteries. This is a considerably higher incidence rate of transposition than the 18 percent rate found in the group with decreased pulmonary flow. Nine of the 10 patients with transposition and increased pulmonary blood flow had intractable congestive heart failure in the 1st 3 months of life. In contrast, only 4 of the 14 patients without transposition and increased pulmonary flow presented with failure. The usual presentation for this latter group was progressive cyanosis at a mean age of 9 months.

Surgical palliation of tricuspid atresia with increased pulmonary blood flow and intractable congestive failure consists of banding the pulmonary artery in the 1st 3 months of life to protect the pulmonary vasculature. Children with increased pulmonary flow, tricuspid atresia and normally related great arteries will probably not require banding as infants but will become cyanotic by age 9 months and require shunting at that time. This was the course in 10 of our 14 patients in this category. The long-term prognosis of these patients who survive initial palliation is probably similar to that of the larger group of children with decreased pulmonary blood flow.

Conclusions and Recommendations

As a result of this experience and the recent work of Fontan and Baudet[1] and others,[7] our present policy in managing children with tricuspid atresia is as follows:

For children less than 10 years of age with increasing cyanosis, we recommend an initial systemic arterial shunt on the side contralateral to the superior vena cava. A Potts shunt is the procedure of choice in the infant less than 6 months of age. The anastomosis is loosely banded to limit its growth. At present we favor a circumference of 26 mm.[8] This size of anastomosis should maintain a child to the age of 10 to 12 years. In children more than 6 months of age, a Potts shunt with banding of the anastomosis or a Blalock-Taussig shunt with proximal arterioplasty[9] is recommended, again on the side contralateral to the superior vena cava.

Children with increased pulmonary blood flow with intractable congestive heart failure require pulmonary arterial banding to control the heart failure and prevent pulmonary vascular disease. Most of these children have transposition of the great arteries and are less than 3 months of age.

Children more than 10 years of age with increasing cyanosis should be carefully selected for either a Glenn shunt or a Fontan procedure. Children of this age with a right ventricular infundibular chamber and an adequate pulmonary valve without a previous arterial shunt and normal pulmonary vascular resistance seem to be ideal candidates for the Fontan procedure.

Children with an inadequate main pulmonary artery, valve and infundibulum and patients with a previous arterial shunt who have a pulmonary vascular resistance greater than 4 units[10] should have a Glenn shunt. Pulmonary arterial size and pressure as well as pulmonary vascular resistance must be within acceptable limits for the Glenn shunt.[11,12] In those few patients who would not tolerate a venous shunt, a second arterial shunt can be a satisfactory alternate procedure. A few patients will fall between these limits, and more experience will be necessary to assess the place of the Fontan operation.

A combination of a systemic arterial shunt to the left lung and a superior vena cava to right pulmonary artery shunt offers a balanced circulation and excellent palliation into adult life. Comparison with the late results of the Fontan procedure will be of interest.

Acknowledgment

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Cardiac Rhabdomyoma: A Clinicopathologic and Electron Microscopic Study

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Cardiac rhabdomyomas are rare tumors of infancy. In a series of 36 patients 78 percent were under 1 year of age, and only one patient was over age 15 years. Ninety percent of the rhabdomyomas were multiple and occurred with nearly equal frequency in the right and left ventricles. Although reportedly infrequent in the atria, rhabdomyomas involved either one or both atria in 30 percent of patients. In 50 percent of patients at least one of the tumor masses was intracavitary and obstructed 50 percent or more of one of the cardiac chambers or valve orifices. Symptoms referable to obstruction of intracardiac blood flow were present in nine patients, none of whom had tuberous sclerosis, and all of whom would appear to have been good surgical candidates. Histologically the rhabdomyomas were composed of classic "spider cells." Electron microscopic studies revealed scattered bundles of myofibrils ringing these cells and radiating toward the center; glycogen was present both free in the cytoplasm and within mitochondria. Distinct intercellular junctions resembling intercalated discs with well defined desmosomes and nexuses were present. Many of the cells contained leptofibrils, arranged either peripherally or in spiraled clusters in the center of the cell. Rhabdomyomas derive from cardiac muscle cells and appear to represent hamartomas rather than true tumors.

The cardiac rhabdomyoma was first described by von Recklinghausen[1] in 1862. In the ensuing years, more than 100 examples of this tumor have been reported, primarily in individual case reports. The pathologic features of cardiac rhabdomyomas have been the subject of several reviews.[2–4] However, these reviews are based on collected published cases in which the accuracy of the original diagnoses could not be critically evaluated. In our experience a variety of tumors, as well as some storage diseases of the heart, have been diagnosed as rhabdomyomas in the past. We therefore limited our review to unequivocal well documented cases of cardiac rhabdomyomas in the files of the Armed Forces Institute of Pathology and did not attempt an exhaustive search of the literature. Although other authors[5–7] have attempted to define the clinical features of the cardiac rhabdomyoma, the number of patients in each of these series is limited because of the relative rarity of the tumor. Thus, many aspects of the histogenesis and clinical course of cardiac rhabdomyoma are yet to be defined.

The material available at the Armed Forces Institute of Pathology offered a unique opportunity to study a large number of well documented cardiac rhabdomyomas. The purposes of our study are (1) to define the characteristics of the cardiac rhabdomyoma with light and electron microscopy, and (2) to establish some correlations between the clinical and pathologic findings in patients with these tumors.

Materials and Methods

Only cases with adequate tissue from the heart and clinical summaries were chosen for inclusion in this study. Of the 36 cases selected, 5 were previously reported as individual cases.[8–12]

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TABLE I

Clinical Features of 36 Patients with Cardiac Rhabdomyomas

Case no.	Age at Time of Death	Sex	Clinical Findings							Other Findings	Duration of Symptoms	Clinical Diagnosis	Cause of Death
			RDS	CHF	Cyan.	Conv.	Mur.	Card. Enl.	ECG Changes				
Group I													
1	SB* (24 g)	M	...	...	...	...	...	...	...	...	...	Toxemia	CR
2	SB* (24 g)	M	...	...	...	...	...	...	...	...	...	—	CR
3	SB* (40 g)	M	...	...	...	...	...	...	...	...	...	—	CR
4	5 min (40 g)	M	—	—	—	—	—	—	—	—	—	Prolapsed cord	CR
5	5 min (40 g)	M	—	—	—	—	—	—	—	—	—	—	CR
6	15 min (40 g)	M	—	—	—	—	—	—	—	—	—	—	CR
7	33 min (36 g)	F	—	—	—	—	—	—	—	Hydrops	—	Hydramnios, P	CR
8	76 min (33 g)	M	—	—	—	—	—	—	—	No spont. resp.	—	P	CR
9	84 min (36 g)	M	+*	+	—	—	—	+	—	Hydrops	—	P	CR
10	3.5 hr (36 g)	F	+*	—	—	—	—	—	—	—	—	P, RDS	Brain hemorrhage
11	6.5 hr (32 g)	M	+*	0	0	0	0	0	—	Placenta previa	6.5 hr	P, RDS	CR
12	18 hr (40 g)	F	+*	—	—	—	—	—	—	Anemia	—	RDS	Hemoperitoneum
Group II													
13	23 hr (40 g)	—	0	0	0	+*	0	0	—	0	8 hr	Brain hemorrhage	TS
14	54 hr (40 g)	M	+	0	+	0	0	0	—	Peritonitis,* jaundice	36 hr	Meconium ileus	Perforated ileum
15	2 mo (40 g)	M	0	0	0	+	0	0	—	Fever*, otitis	3 days	Meningitis	Meningitis
16	4 mo	M	+	0	0	+	0	0	—	Diarrhea*	7 days	Gastroenteritis	TS
17	9 mo	M	0	0	0	+*	—	—	—	0	5 hr	Convulsive state	TS
18	13 mo	F	0	0	0	+*	0	0	PAC	0	11 mo	TS	TS
19	17 mo	F	0	0	0	+*	0	0	—	0	17 mo	Convulsive state	TS
20	3.5 yr	F	0	0	0	+*	0	0	—	0	40 mo	Glioma	TS
21	5 yr	F	0	0	0	+*	0	—	—	0	2 yr	Brain-stem tumor	TS
22	5 yr	M	0	0	0	+*	0	+	—	0	3 yr	Convulsive state	TS
23	20 yr	M	0	0	0	0	0	—	—	Fever*	1 wk	Tetanus	Tetanus
Group III													
24	36 hr (40 g)	M	+	0	+*	0	0	0	—	0	12 hr	RDS	CR
25	40 hr (32 g)	F	+	0	+*	0	0	—	—	0	40 hr	P, RDS	HMD
26	68 hr (40 g)	M	+	0	+*	0	0	+	—	0	68 hr	CHD	CR
27	4 days (40 g)	M	+*	—	+	0	—	+	—	0	4 days	RDS	CR
28	5 days (40 g)	M	+	0	+*	0	S, ch	0	PAC	Fever	4 days	Atrial tumor	CR
29	11 days (40 g)	M	+	—	+*	0	±	+	LVH	0	10 hr	PDA,septicemia	CR
30	13 days (40 g)	F	+	+	+*	0	0	+	AF, VT	0	9 hr	CHD	CR
31	1 mo (40 g)	F	+*	+	+	0	0	+	—	0	9 hr	CHD	CR
32	4.5 mo	M	+	+	+*	0	S	+	LVH, IRBBB	0	4 mo	CHD, EFE	EFE
33	7 mo	—	0	0	0	0	S	0	—	Diarrhea*	2 mo	Failure to thrive	CR
34	8 mo	M	+	+	+	0	S, ch	+*	VT, ST	0	8 mo	CHD, VSD	CHD
35	3 yr	M	0	0	0	0	S, ch*	+	VT, IRBBB, S-T-T	Tumor (CC)	3 yr	Cardiac tumor	CR
36	9 yr	M	0	0	0	0	0	0	VF*	0	6 wk	Coma	CR

*Presenting symptom.

0 = finding absent; + = finding present; ± = questionable finding; — = information not available.

AF = atrial fibrillation; Card. Enl. = cardiac enlargement on chest roentgenogram; CC = cardiac catheterization; ch = changing in intensity; CHD = congenital heart disease; CHF = congestive heart failure; Conv. = convulsions; CR = cardiac rhabdomyoma; Cyan. = cyanosis; ECG = electrocardiographic; EFE = endocardial fibroelastosis; g = gestational age in weeks; HMD = hyaline membrane disease; IRBBB = incomplete right bundle branch block; LVH = left ventricular hypertrophy; Mur. = murmur; P = prematurity syndrome; PAC = premature atrial contractions; PDA = patent ductus arteriosus; RDS = respiratory distress syndrome; S = systolic; SB = stillborn; spont. resp. = spontaneous respirations; S-T-T = nonspecific S-T segment and T wave changes; TS = tuberous sclerosis; VF = ventricular fibrillation; VSD = ventricular septal defect; VT = ventricular tachycardia.

The clinical records and necropsy reports were analyzed in each case. Sections of the heart were cut from the paraffin blocks or wet tissue and stained with hematoxylin eosin, the periodic acid-Schiff reaction and oil red O. Whenever the heart was available, additional sections were taken in a search for microscopic rhabdomyomas. The following histologic findings had to be present before the "tumor" was accepted as a rhabdomyoma: (1) "spider cells," (2) identifiable cross striations, and (3) a positive periodic acid-Schiff stain. Criteria to establish a clinical diagnosis of cardiac rhabdomyoma have not been formulated, although the frequent occurrence of these tumors in patients with tuberous sclerosis is well recognized.[2,4]

In the absence of fresh tissue, electron microscopy was performed on tissue from seven hearts that were fixed and stored in 10 percent formalin for several years. The tissue blocks were rinsed with 0.1 molar phosphate buffer, pH 7.4, and then fixed with 2 percent glutaraldehyde in phosphate buffer, pH 7.4, for 2 hours. After rinsing with phosphate buffer, the blocks were postfixed with phosphate-buffered (pH 7.4) 1 percent osmium tetroxide for 1 hour, dehydrated in graded alcohols and embedded in Epon 812. Ultrathin sections were cut on an LKB ultramicrotome. The grids were stained with uranyl acetate and lead citrate[13] and examined with a JEOL 100B electron microscope.

Results

Clinical Features

The clinical findings in the 36 patients are summarized in Table I. Seventy-eight percent (Cases 1 to 17 and 24 to 34) were dead by age 1 year. However, 53 percent of patients (Cases 1 to 14 and 24 to 28) were dead by age 1 week, and eight of these (Cases 1 to 8) either were stillborn or died in the 1st minutes of life. Only one patient (Case 23) was over age 10 years. There was approximately a 2:1 predominance of male over female patients (22 male versus 12 female patients); data concerning sex were not available for 2 patients (Cases 13 and 33). Patients 21 and 22 were siblings.

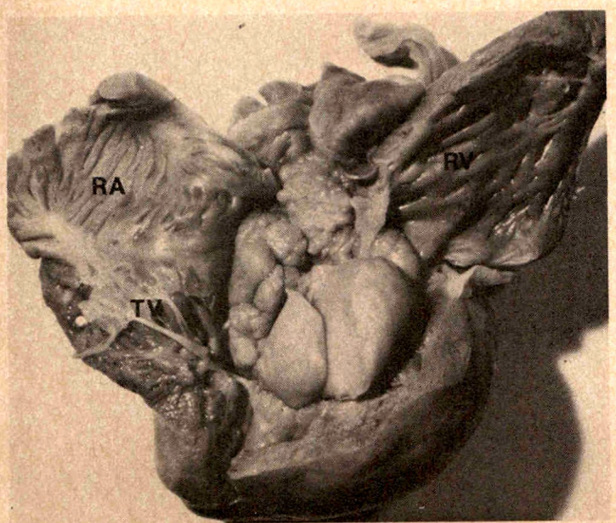

FIGURE 1. Case 4. Intracavitary rhabdomyoma causing both right ventricular inflow and outflow obstruction. This infant died minutes after birth. RA = right atrium; RV = right ventricle; TV = tricuspid valve.

Location of tumors: In attempting to establish clinicopathologic correlations, two factors were of particular importance: whether the tumors were solitary or multiple, and whether they were intracavitary (Table II). Only three patients had solitary tumors; in Patients 27 and 34 the tumors were located in the left ventricular

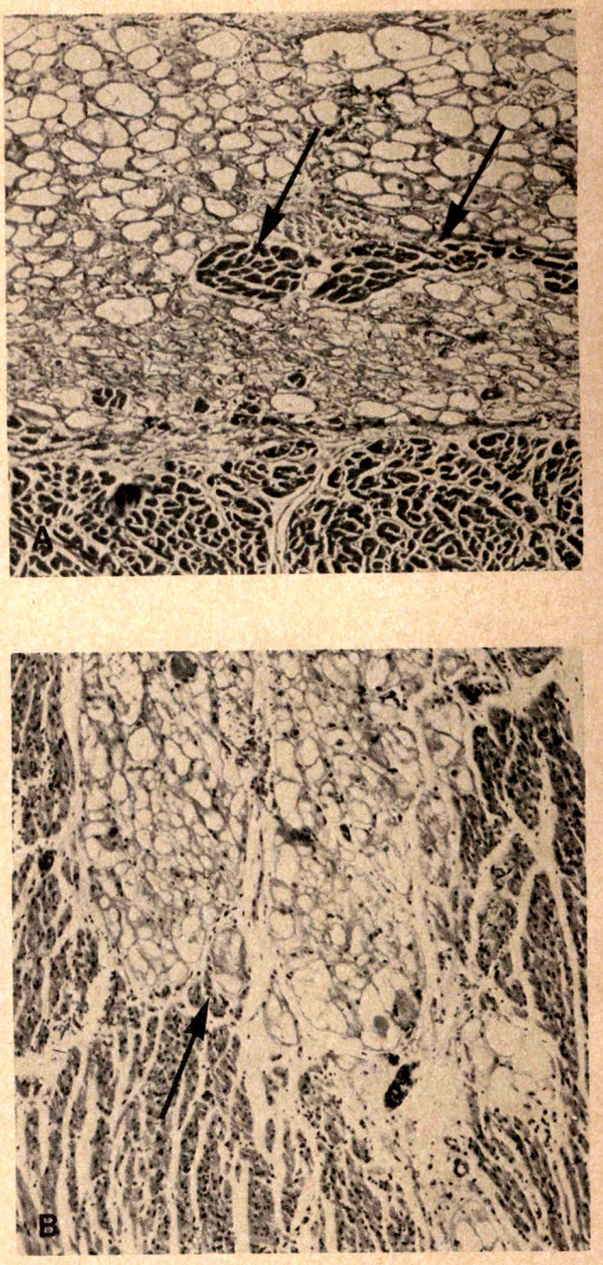

FIGURE 2. Case 36. Photomicrographs. **A,** small rhabdomyoma beneath the endocardium of the left ventricle in a 9 year old child. The tumor has apparently interrupted a distal ramification of the left bundle (**arrows**), which on serial sections is in continuity with the His bundle. The child was admitted with ventricular fibrillation and died suddenly. **B,** small rhabdomyoma in the left ventricular free wall. The mass is circumscribed but not encapsulated and appears to merge with the surrounding muscle (**arrow**). (Hematoxylin-eosin ×56 [**A**] and ×40 [**B**].)

wall, and in Patient 35 in the ventricular septum. The remaining patients (92 percent) had multiple rhabdomyomas. Although the left ventricle was the most frequent location of the rhabdomyomas in our study (100 percent), the tumor nodules were also located in the right ventricle of 26 patients (81 percent). In 11 patients (30 percent) rhabdomyomas involved the atria, the right atrium in 5, the left atrium in 3 and both atria in 3. Tumor nodules were beneath the epicardium in 6 patients (Cases 9, 12 and 16 to 19) (17.5 percent) and beneath the endocardium in 12 (Cases 4, 14, 16 to 18, 20 to 23, 25, 33 and 36) (33 percent). Intracavitary rhabdomyomas with greater than 50 percent obliteration of one of the cardiac chambers (Fig. 1) or cardiac valve orifices were found in 18 patients (50 percent). The intracavitary tumors were singular in 14 of the 18 patients.

Group I: On the basis of clinical findings, the 36 patients were classified in three distinct groups. Patients

TABLE II

Necropsy Findings in 36 Patients with Cardiac Rhabdomyomas

Case no.	Cardiac Weight (g) (expected)	Gross Anatomic Features of Tumor Nodules: Location	Total no.	Size (mm)	Obst.	Microscopic Features of Tumor Nodules: Spider Cells	Str.	Ca^{++}	Fibr.	EMH	TS	Other Findings
					Group I							
1	5.9 (6.2)	RV, LV, VS	6	1–2	0	+	+	0	0	0	0	0
2	10.5 (6.2)	VS(IC)	3	5–24	MV, TV	+	+	+	0	0	0	0
3	34 (23)	RA(IC), LV	6	1–18	FO, TV	+	+	0	0	0	0	0
4	35 (23)	RV(IC), LV	8	2–10	RVC	+	+	0	0	0	—	0
5	145 (23)	LA(IC), RV, LV	5	2–35	MV	+	+	0	+	+	—	0
6	– (23)	RV(IC), LV(IC)	3	40	MV, TV	+	+	+	+	+	+	0
7	31 (18)	RA(IC), RV(IC), LV	6	3–30	TV	+	+	0	+	+	0	0
8	65 (14)	RV, LV(IC)	5	2–40	LVC	+	+	0	+	+	+	Annular pancreas
9	55 (18)	RV, LV(IC)	6	3–28	LVC	+	+	0	+	+	—	0
10	– (18)	RA, LV	6	1–5	0	+	+	0	0	+	0	0
11	16 (14)	RV(IC), LV(IC)	5	2–22	MV	+	+	0	0	+	0	0
12	– (21)	LV	4	2–13	0	+	+	0	0	0	+	Angiolipomas
					Group II							
13	– (23)	RV, LV	8	1–3	0	+	+	0	0	0	+	0
14	– (23)	RA, LA, RV, LV	12	2–10	0	+	+	0	0	0	0	Perforated ileum, ureteral stricture
15	28 (27)	RV, LV	6	2–5	0	+	+	0	0	0	0	Pneumococcal meningitis
16	34 (31)	RA, LA, RV, LV	Num.	2–8	0	+	+	0	0	0	+	0
17	48 (45)	RV, LV	Num.	2–10	0	+	+	0	0	0	+	0
18	60 (49)	LV	3	5–20	0	+	+	0	0	0	+	0
19	65 (50)	RA, LA, RV, LV	20	1–5	0	+	+	0	+	0	+	0
20	70 (66)	RV, LV	8	2–15	0	+	+	0	+	0	+	Angiomyolipomas
21	85 (85)	RV, LV	3	4–10	0	+	+	0	0	0	+	Angiomyolipomas
22	95 (85)	RV, LV	4	4–12	0	+	+	0	+	0	+	Renal hamartoma
23	348 (312)	RV, LV	Num.	3–15	0	+	+	0	0	0	0	0
					Group III							
24	– (23)	RV, LV(IC)	7	2–48	LVC	+	+	0	+	+	0	Renal hamartoma
25	17 (13)	RV, LV	6	1–4	0	+	+	0	0	0	—	0
26	64 (23)	RV, VS, LV(IC)	10	2–30	LVC	+	+	0	+	+	0	Renal cysts
27	– (23)	LV(IC)	1	15	MV	+	+	0	0	0	0	0
28	24 (23)	RA, RV(IC), LV	5	2–10	PV	+	+	0	0	0	0	Cleft palate, hypoplasia of mandible
29	46 (21)	LV, VS(IC)	5	2–30	MV	+	+	0	+	+	0	0
30	53 (21)	RV, VS, LV(IC)	6	2–25	MV	+	+	0	0	0	—	0
31	75 (21)	LA(IC), LV	2	6–65	MV	+	+	0	0	0	0	ASD
32	174 (31)	RA, LV	4	2–15	0	+	+	0	+	+	0	EFE, ASD
33	30 (40)	RV, LA, LV(IC)	12	2–20	AoV	+	+	0	0	0	—	0
34	48 (44)	LV	1	4	0	+	+	0	0	0	0	Goiter, PDA, VSD, ICD
35	73 (59)	LV(IC), VS	1	30	LVC	+	+	0	0	0	0	0
36	170 (115)	LV, VS	6	3–15	0	+	+	0	0	0	0	0

0 = finding absent; + = finding present; — = information not available.

ASD = atrial septal defect; AoV = aortic valve; Ca^{++} = calcium deposits as shown by von Kossa stain; EFE = endocardial fibroelastosis; EMH = extramedullary hematopoiesis; Fibr. = fibrosis; FO = foramen ovale; IC = intracavitary; ICD = incomplete differentiation (dysplasia) of mitral and tricuspid valves; LA = left atrium; LV = left ventricle; LVC = left ventricular cavity; MV = mitral valve; Num. = too numerous to count; Obst. = 50 percent obstruction of a valve orifice or cardiac chamber by tumor; PDA = patent ductus arteriosus; PV = pulmonary valve; RA = right atrium; RV = right ventricle; RVC = right ventricular cavity; Str. = striations; TS = tuberous sclerosis; TV = tricuspid valve; VS = ventricular septum; VSD = ventricular septal defect.

in Group I (Cases 1 to 12) were stillborn or died within the 1st 24 hours of life. Clinical information was fragmentary in this group. Four patients (Cases 9 to 12) who survived long enough for clinical data to be recorded presented with respiratory distress. Seventy-five percent of the patients in Group I had an intracavitary rhabdomyoma and presumably died as a result of obstruction to intracardiac blood flow. Three patients died of other causes (Tables I and II) and either their condition was correctly diagnosed or they died before clinical findings could be assessed. Patients 6, 8 and 12 had tuberous sclerosis. The brain was not examined in Patients 4, 5 and 9. The incidence rate of tuberous sclerosis in the Group I patients whose brain was examined was 33 percent.

Group II: This group consisted of 11 patients (Cases 13 to 23), none of whom presented with clinical findings referable to the heart, and only three of whom (Cases 14, 18 and 22) had any clinical cardiac findings. All 11 had multiple rhabdomyomas, but no intracavitary tumors were found in this group. Seventy-three percent of the patients had tuberous sclerosis. In Patients 14, 15 and 23 the rhabdomyomas were incidental and completely unsuspected findings at necropsy.

Group III: Thirteen patients (Cases 24 to 36) constituted Group III. All had significant clinical cardiac findings at the time of presentation. Nine patients (69 percent) had an intracavitary rhabdomyoma that appeared to obstruct intracardiac blood flow; in two patients (Cases 28 and 35) the diagnosis of a cardiac tumor was made before death on the basis of a systolic murmur of changing intensity. No other necropsy findings were present in these nine patients to explain the clinical signs and symptoms. Patients 25, 32, 34 and 36 had multiple rhabdomyomas, none of which were intracavitary; two (Cases 32 and 34) had congenital heart disease; a third patient (Case 25) was a premature infant with a severe respiratory distress syndrome. None of the patients in Group III had tuberous sclerosis, although the brain was not examined in Patients 24, 30 or 33.

One patient (Case 36) in Group III presented with syncope and episodic, eventually fatal, ventricular fibrillation. He had no cardiomegaly by chest roentgenogram and no evidence of congestive heart failure, cyanosis, cardiac murmur or dyspnea. At necropsy, multiple small intramural rhabdomyomas were noted. Many of these were subendocardial and compressed the fasciculi of the left bundle branch and distal subendocardial Purkinje network (Fig. 2).

Tuberous sclerosis: Eleven patients (Cases 6, 8, 12, 13 and 16 to 24) in this series had tuberous sclerosis, an incidence rate of 31 percent, but in six patients the central nervous system was not examined. Thus, the incidence rate of tuberous sclerosis associated with rhabdomyomas in the total of 30 patients whose brain was examined was 37 percent. Examination of the brain in 13 of the 18 patients with intracavitary rhabdomyomas disclosed tuberous sclerosis in two patients (15 percent) (Cases 6 and 8). In contrast, of 17 patients with solely intramural rhabdomyomas whose brain was examined, 9 (53 percent) had tuberous sclerosis. To the end of 1970, autopsy studies were performed in 40 patients with tuberous sclerosis at this institution. Among these there were 12 patients with cardiac rhabdomyomas. Thus, the incidence rate of rhabdomyoma in these patients with tuberous sclerosis is 30 percent, or approximately the same as the incidence rate (37 percent) of tuberous sclerosis in our series of patients with cardiac rhabdomyoma.

Congenital anomalies: Five patients (14 percent) in our series had congenital anomalies. Two of these had symptomatic cardiac anomalies, as previously men-

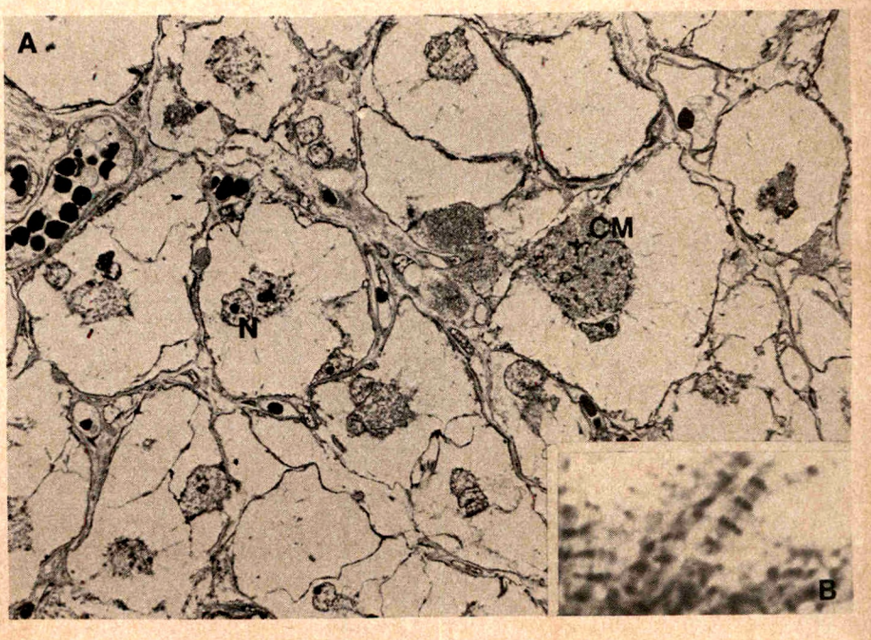

FIGURE 3. A, the classic cells of the rhabdomyoma have centrally placed cytoplasmic masses (CM) with eccentric nuclei (N) and strands of cytoplasm that extend to the periphery of the cell, the so-called "spider cell." **B,** at high magnification cross striations can usually be demonstrated in the radiating strands of cytoplasm or adjacent to the cell membrane. (Toluidine blue ×500 [**A**] and phosphotungstic acid-hematoxylin ×1,320 [**B**].)

tioned. The remaining three patients (Cases 8, 28 and 31) had minor anomalies that were not life-threatening. Angiomyolipomas and hamartomas of the kidneys were found in five other patients (14 percent), four of whom had tuberous sclerosis.

Pathologic Findings

Microscopic findings (Table II): These were similar in the rhabdomyomas of all 36 patients. The tumors were circumscribed but not encapsulated and were easily distinguished from the surrounding myofibers (Fig. 2B). They ranged in diameter from several microns to several centimeters. The cells constituting these tumors tended to be larger (up to 80 μ in diameter) than the surrounding myocardial fibers and appeared vacuolated. Occasional cells were smaller and had an eosinophilic granular cytoplasm. Glycogen was present in all of the rhabdomyoma cells but was abundant only in tissues fixed in alcohol.[14] Classic "spider cells" were characterized by a centrally located mass of finely granular cytoplasm with thin, elongated projections and slender myofibrils extending to the periphery (Fig. 3A); although rare, they were found in every case. More frequently the nucleus was displaced to the periphery of the cell and cross striations were identified around the periphery of the cell (Fig. 3B). Stromal collagen was usually scant, although in several tumors there was abundant collagen. In two cases there were microscopic foci of calcification within rhabdomyoma cells (Fig. 4A). Foci of extramedullary hematopoiesis were identified in the majority of tumors from the newborn group (Fig. 4B).

FIGURE 4. A, microscopic focus of calcium deposition (**arrows**) within rhabdomyoma cells. **B,** many of the rhabdomyomas in newborns (see Table II) contained collections of nucleated red cells (**arrows**), myelocytic precursor cells, and occasional megakaryocytes, consistent with extramedullary hematopoiesis. (Von Kossa ×530 [**A**] and Giemsa ×440 [**B**], both reduced by 12 percent.)

Electron microscopy: Although the fixation of our material was not ideal for electron microscopy, the preservation of structural detail was adequate to make some observations concerning certain subcellular components of rhabdomyoma cells. The ultrastructural appearance was basically similar in the seven tumors examined. The cytoplasm was typically concentrated around the periphery of the cell, and the center of the cell contained only scattered glycogen granules of the monoparticulate or β type. In one case more glycogen was preserved, and the centers of the cells were filled with particles of glycogen. The rim of cytoplasm against the cell membrane contained only scattered mitochondria, myofibrils and numerous leptofibrils with a periodicity of 1,500 to 1,700 Å. In scattered cells there were central masses of cytoplasm that were connected to the periphery by strands of cytoplasm. These central masses often contained complexes of leptofibrils in a whorled or ball-like configuration (Fig. 5), clusters of fragmented sarcomeric units (Fig. 6), fragments of membranes that probably were derived from mitochondria, and deposits of material resembling that in Z bands. The radiating strands of cytoplasm also contained leptofibrils, segments of sarcomeres, scattered mitochondria and segments of dilated endoplasmic reticulum. The nuclei were ovoid, with peripherally clumped chromatin, and were located either adjacent to the central masses of cytoplasm or peripherally against the cell membrane. The myofibrils were narrow, coursed parallel to the plasma membranes, often showed branching, and were composed of normal-appearing thick and thin myofilaments; the fine structure of the Z bands was poorly preserved. There was no discernible relation of mitochondria to sarcomeres or leptofibrils. Scattered segments of endoplasmic reticulum were identified, but no T tubules were found.

The cells were joined to one another over long segments of their plasma membranes by junctions that resembled intercalated discs (Fig. 7). The junctions had desmosomes, zonulae adherens and undifferentiated segments; nexuses were also present but infrequent.

Many of the cells contained accumulations of Z band-like material (Fig. 6 and 7), often in apposition to the cell membrane. Intramitochondrial glycogen and calcium deposits free in the cytoplasm were also found (Fig. 8).

The stroma consisted of scattered bundles of collagen and strands of long-spacing collagen with a periodicity of approximately 1,200 Å. The strands of long-spacing collagen were most frequently observed in apposition to the cell membrane. Normal-appearing capillaries were found throughout.

Discussion

Clinicopathologic Correlations

Cardiac rhabdomyoma is almost exclusively a tumor of infancy and early childhood. In our series, 70 percent of the patients were dead by the end of the 1st year of life, and 92 percent were dead by age 5 years. Only three patients survived past 5 years of age, and the oldest of these was 20 years. Kidder[15] reported somewhat lower figures: 60 percent dead within 1 year and 80 percent dead within 5 years.

Intracavitary versus intramural tumors: The high incidence rate of intracavitary rhabdomyomas in our

patients was an unexpected finding. Although intracavitary rhabdomyomas have been reported,[6,7,16] their significance has not been fully appreciated. Intracavitary tumors were obviously the cause of death in seven of eight patients in Group I who either were stillborn or survived for only a few minutes after birth. In these patients the tumor filled at least 50 percent of one or more cardiac chambers and produced marked obstruction to blood flow. Although one or more of the cardiac valves were often displaced or deformed by encroaching tumor mass, we did not find a rhabdomyoma that invaded and replaced or arose from a cardiac valve.

Nine of the 13 patients with cardiac symptoms (Group III) also had intracavitary rhabdomyomas with partial obstruction to blood flow. The intracavitary

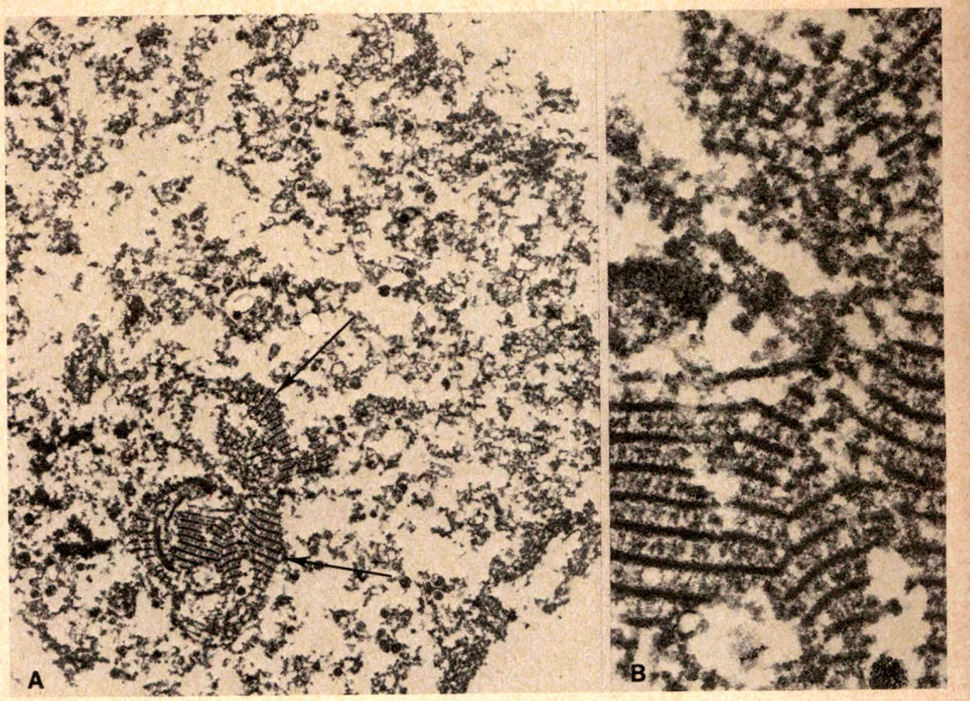

FIGURE 5. A, central cytoplasmic mass containing disorganized fibrillar material and a cluster of spiralled leptofibrils (**arrows**). **B,** high magnification of the leptofibrils. These structures have a periodicity of 1,600 Å. (×7,500 [**A**] and 30,000 [**B**], both reduced by 21 percent.)

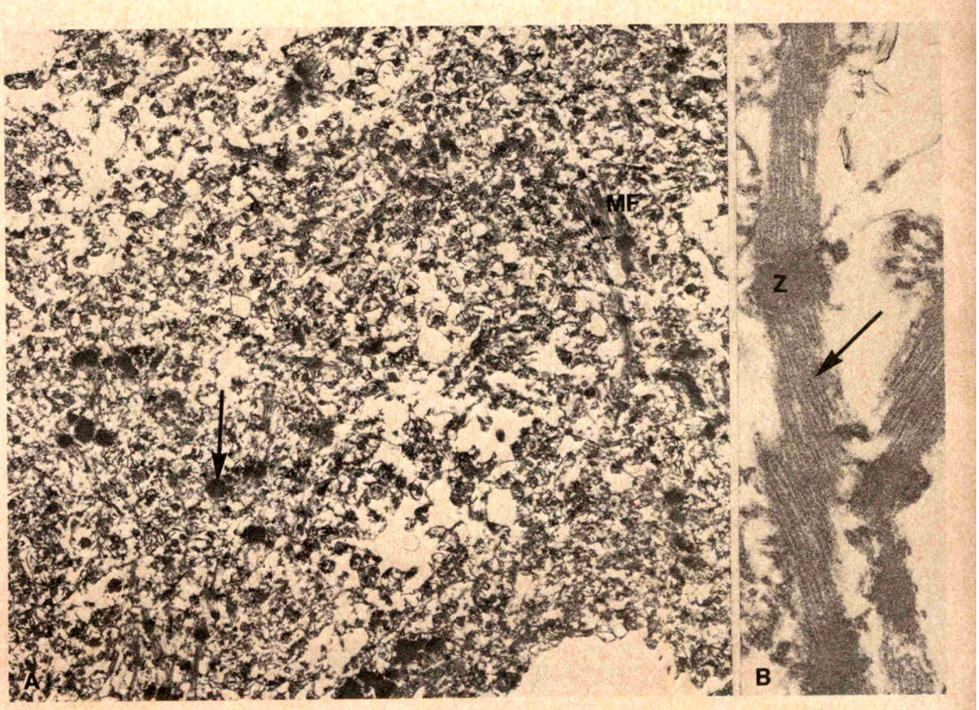

FIGURE 6. A, electron micrograph of a central cytoplasmic mass such as that shown in Figure 3. This mass contained small short rudimentary myofibrils (MF), clumps of Z band-like material (**arrow**) and disorganized membranous and fibrillar material. **B,** view at higher magnification of myofibrils in rhabdomyoma cell illustrating Z bands (Z) and thick and thin filaments (**arrow**). (×7,500 [**A**] and 30,000 [**B**], both reduced by 21 percent.)

tumors appeared to be responsible for the clinical cardiac findings. Unfortunately, angiographic evidence of cavitary obstruction and documentation by cardiac catheterization of a marked hemodynamic gradient were obtained in only one patient. The findings in this patient simulated subaortic stenosis, an occurrence previously described in cardiac rhabdomyoma.[17,18] Three other patients had systolic murmurs of changing intensity, a finding suggestive of an intracavitary mass. The clinical cardiac, electrocardiographic and roentgenographic findings in these nine patients are not specific for cardiac rhabdomyoma. They are similar to the cardiac findings now well documented for cardiac myxoma[19,20] and probably result from an intracavitary mass. In our experience, however, any infant or child less than 5 years of age presenting with findings sug-

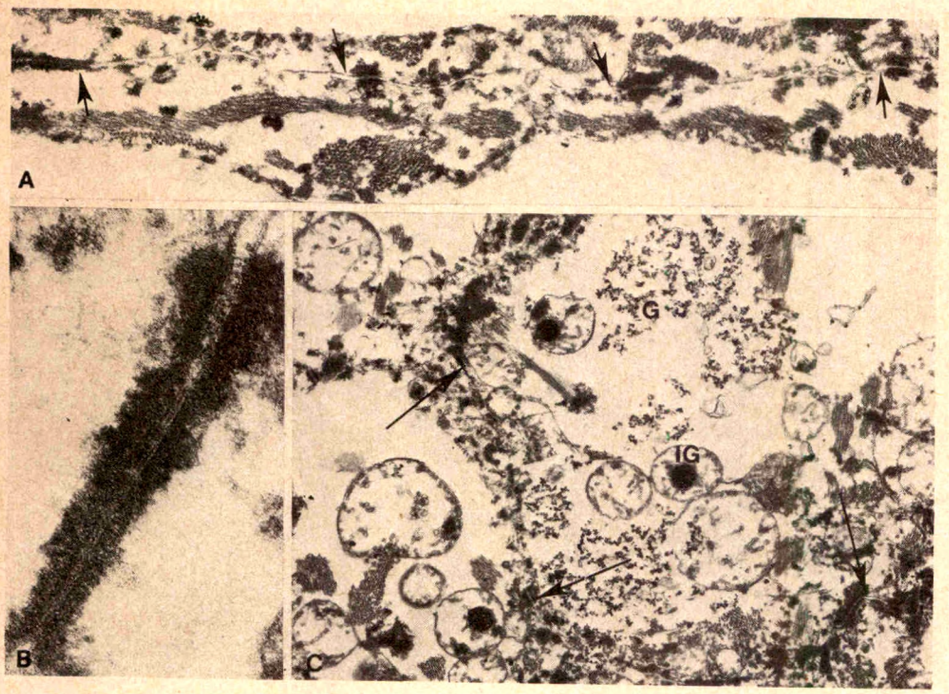

FIGURE 7. Junctional structures in rhabdomyoma cells. **A,** the intercellular junction between two rhabdomyoma cells (**arrows**) is associated with a thin layer of myofilaments on each of its sides. **B,** highly magnified view of the nexus shown in **A.** Note the close approximation of the leaflets of the plasma membrane, forming quintuple layered junction. **C,** intercellular junction (**arrows**) similar to, but more highly convoluted than that in **A.** Glycogen deposits (G) are seen in the cytoplasm of one of these cells, and the intramitochondrial glycogen (IG) is present in both cells. (×22,500 [**A**], 125,000 [**B**] and 15,000 [**C**], all reduced by 21 percent.)

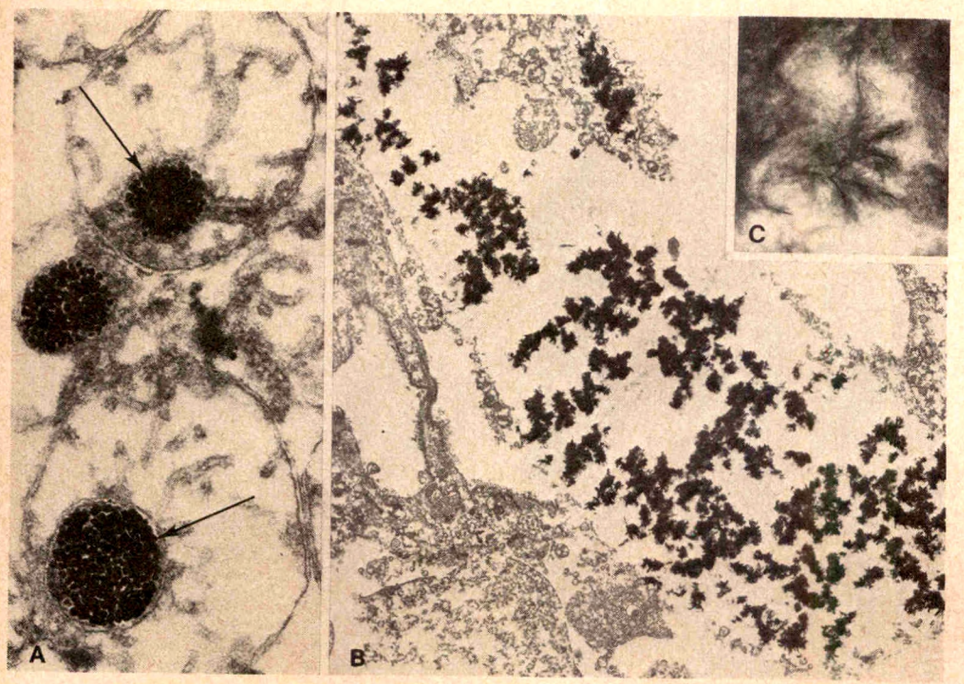

FIGURE 8. A, high magnification of intramitochondrial glycogen deposits (**arrows**). The deposits are in the intracristal compartment and are composed of monoparticulate glycogen. **B,** calcium deposits within the rhabdomyoma cells are free within the cytoplasm and do not appear to be associated either with mitochondria or membrane material. **C,** high magnification of the calcium deposits shown in **B.** Note the needle-like crystalline array of the deposits. (×57,000 [**A**], 6,500 [**B**] and 78,000 [**C**], all reduced by 21 percent.)

gestive of an intracavitary mass probably has a rhabdomyoma rather than a myxoma. We have seen only one child less than 5 years of age (4 years old) with a cardiac myxoma (Fenoglio and McAllister, unpublished observations).

None of our patients with strictly intramural rhabdomyomas had congestive heart failure. This observation is in accord with the concept that hemodynamic obstruction, rather than replacement of myocardium by tumor, is the cause of findings suggestive of congestive heart failure in patients with cardiac rhabdomyomas.[7]

Surgical resection: In five reported cases, cardiac rhabdomyomas were resected surgically with good results.[4,18,21,22] The rhabdomyomas were at least partially intracavitary in all five patients and produced symptoms related to obstruction of intracardiac blood flow. These symptoms were relieved by surgery. Two patients had multiple rhabdomyomas in the ventricular myocardium, and in a third only the intracardiac portion of the rhabdomyoma was resected. Anatomic data were not given for the other two patients. All patients did well postoperatively, and one patient was alive and well 2 years postoperatively.[21] Adequate follow-up information was not available in the remaining four patients. Although one patient[21] had a low mentality, there was no evidence of tuberous sclerosis in these five patients.

At least 25 percent of our patients (Cases 24, 26 to 31, 33 and 35) would appear to have been good surgical candidates. All nine of these patients had clinical cardiac findings and intracavitary rhabdomyomas. Presumably they were symptomatic because of obstruction of intracardiac blood flow by the rhabdomyoma. None of these patients had tuberous sclerosis. Although the rhabdomyomas were multiple in eight patients, we do not consider this to be a contraindication to surgical relief of intracavitary obstruction. This is suggested by the limited surgical experience discussed earlier and by the fact that the capacity for growth of rhabdomyomas appears to be limited. We did not identify mitotic figures in any cardiac rhabdomyoma. We believe that, like adult cardiac muscle, rhabdomyoma cells lose the ability to divide and grow only by increasing cell mass and size.

Tuberous sclerosis: The incidence rate of tuberous sclerosis has been reported as 50 percent or higher in patients with rhabdomyomas.[2] After elimination of patients whose brain was not examined, only 37 percent of our series had associated tuberous sclerosis. Many of our patients were stillborns or newborns, and although tuberous sclerosis has been diagnosed in stillborn infants,[23] establishing the diagnosis in this age group is difficult. This may partially account for the lower incidence rate in our series. We found, however, that tuberous sclerosis is more frequent in patients with solely intramural rhabdomyomas and in patients without clinical cardiac findings. Tuberous sclerosis was present in 50 percent of patients with solely intramural rhabdomyomas and in 73 percent of patients in Group II. By contrast, only 33 percent of Group I and none of the patients in Group III had tuberous sclerosis.

Thus, the demonstration of an intracardiac mass in a symptomatic patient under age 5 years is strongly suggestive of a rhabdomyoma. Despite the overwhelming likelihood that these tumors are multiple, it is probable that a single intracavitary rhabdomyoma is responsible for the clinical symptoms and that the patient does not have tuberous sclerosis. We suggest that such patients are candidates for cardiac surgery.

Structural Aspects of Cardiac Rhabdomyomas

Although only limited ultrastructural observations could be made in this study, they demonstrate conclusively that rhabdomyoma cells have features, namely sarcomeres and specialized intracellular junctions, that are typical of cardiac muscle cells. As discussed later, rhabdomyoma cells clearly differ from Purkinje fibers[24,25] and working myocardial cells.[26,27] We do not consider rhabdomyomas abnormal proliferations of these differentiated cell types. The rhabdomyoma is also not a localized form of glycogen storage disease.[28,29] In glycogen storage disease with cardiac involvement (types II, III and IV), the sarcomeres are lost or compressed around the periphery of the cardiac muscle cells,[29] but these cells, although greatly distended by the glycogen deposits, maintain their cylindrical shapes and have intercalated discs at their ends. Thus, the preservation of a relatively normal cell shape distinguishes glycogen-laden cardiac muscle cells in glycogen storage disease from rhabdomyoma cells.

Cardiac rhabdomyoma cells resemble the P cells of the sinoatrial node[30,31] and normal cardiac myoblasts[32] in that they have intercellular junctions randomly oriented along the periphery of the cells. The junctions of P cells, unlike those of rhabdomyoma cells, lack nexuses. Cardiac myoblasts, both in vivo and in culture, are ovoid or stellate, thus differing from cardiac rhabdomyoma cells. Sarcomeres are absent from the most primitive cardiac myoblasts (that is, presumptive myoblasts) and are first recognized in myoblasts near the plasma membranes in association with accumulations of material resembling that in Z bands.[32,33] Although this arrangement is similar to that in rhabdomyoma cells, the latter also have numerous leptofibrils.

The presence of large numbers of leptofibrils, although fascinating, offers no clue to the origin of the rhabdomyoma. Leptofibrils have been observed in Purkinje fibers and myocardial cells in many animal species[34,35] and in skeletal[36] and cardiac muscle in man (Ferrans, unpublished observations). The significance of these structures is unknown.

Cardiac versus extracardiac rhabdomyoma: The cardiac rhabdomyoma does resemble, in some aspects, extracardiac rhabdomyoma. Although extracardiac (that is, skeletal muscle) rhabdomyoma cells never have cell junctions, they are composed of normal myofibrillar constituents in a haphazard array.[37–42] The electron microscopic appearance of extracardiac rhabdomyomas varies greatly from case to case. In at least two reported cases[37,40] the cells were found to be rounded, with abundant glycogen and peripherally placed remnants of sarcomeres, not unlike cardiac rhabdomyoma cells;

however, extracardiac rhabdomyomas with branching cells filled with disorganized sarcomeres also have been reported.[41] Extracardiac rhabdomyomas contain accumulations of Z band-like material,[38] and intranuclear and intramitochondrial inclusions that resemble glycogen also have been noted in these tumors.[40,42] All the cardiac rhabdomyomas in our series contained more glycogen and fewer contractile elements than has been reported in extracardiac rhabdomyomas. However, there was considerable variation in the number of sarcomeres in the cells in our tumors. At least one cardiac rhabdomyoma contained only scattered sarcomeres at the periphery of the cells, whereas others had sarcomeres both peripherally and in the central mass. We found no rhabdomyomas with branching cells filled with sarcomeric units.

Although we found no T tubules in cardiac rhabdomyoma cells, preservation of ultrastructural detail was poor, and further studies of this are needed. T tubules have been found in skeletal muscle rhabdomyomas.[37,40] Certain types of adult cardiac muscle cells (Purkinje fibers, specialized conducting cells and many atrial muscle cells) in adult man and other mammals lack T tubules. Furthermore, T tubules develop in ventricular muscle cells only after birth.[43] Because of this, we believe that cardiac rhabdomyoma cells differentiate from primitive muscle cells at a time when the latter lack T tubules.[32,33] This conclusion is in accord with the observations that both cardiac rhabdomyoma cells and primitive cardiac muscle cells have their contractile elements subjacent to the plasma membranes and their intercellular junctions randomly located all along their periphery.

Hamartoma or true neoplasm? The preponderance of multiple as opposed to solitary cardiac rhabdomyomas and their most frequent occurrence in infants suggests that the cardiac rhabdomyoma is a hamartoma or malformation rather than a true neoplasm. The clinical behavior and the microscopic appearance of these tumors suggest that rhabdomyoma cells eventually lose their ability to divide. A similar loss of mitotic activity occurs in normally differentiated human cardiac muscle cells soon after birth. The rhabdomyoma cells appear to undergo arrest of development and to lose the ability to differentiate fully. These cells do not appear to have become dedifferentiated, as have many neoplastic cells, but rather to have differentiated in an aberrant pathway from cardiac myoblasts. We propose that cardiac rhabdomyomas are tumor-like malformations that should be regarded as fetal hamartomas.

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Atrial Myxoma in a Family

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A family is described in which the mother and three of seven children had atrial myxoma. The mother had biatrial myxoma; surgical treatment resulted in massive intraoperative embolization and death. Surgery was successful in two sons with left atrial myxoma and systemic arterial embolization. A third son had calcified right atrial myxoma with destruction of the tricuspid valve and episodes of syncope and pulmonary embolism; surgery, including valve replacement, was successful. The mother's father and a brother had died suddenly without a definite diagnosis. The family data are consistent with dominant transmission. The possibility of finding affected relatives should be borne in mind when studying patients with atrial myxoma.

Primary tumors of the heart are rare. More than half of them are myxomas, which are encountered in about 0.01/1,000 autopsies.[1] Originally described in 1845 by King[2] the condition was first diagnosed during life in 1952 by Goldberg et al.[3] using angiography. Bahnson and Newman[4] and Crafoord[5] were the first to report successful surgical removal of, respectively, a right and left atrial myxoma. Since then the diagnosis of cardiac myxoma in a living person has become less rare. Recently two cases of cardiac myxoma in siblings[6,7] were described. This report describes a family in which the mother and three of seven children were operated on for atrial myxoma.

Case Histories

Case 1: A.E.K., a farmer's wife born in 1931, had had six deliveries between 1949 and 1959 with one pair of twins. As a child she had been healthy, but at age 19 years she began to have brief attacks of unconsciousness. Secondary epilepsy was diagnosed, and the condition was controlled with conventional drug therapy. In 1959 the erythrocyte sedimentation rate was 50 mm in 1 hour without any obvious cause. In February 1963 she had a disease with fever, vague arthralgia, faint early diastolic heart murmur and mild cardiomegaly. The antistreptolysin titer was slightly increased. The symptoms persisted for many weeks despite intensive antibiotic therapy. On hospital admission the erythrocyte sedimentation rate was 120 mm in 1 hour and decreased later to 65 mm in 1 hour. A presumptive diagnosis of rheumatic fever with carditis was made. In February 1964 the patient's exertional dyspnea increased and she was sent to the University Central Hospital in Helsinki for further examinations.

On physical examination, she appeared to be a pale asthenic woman in poor general condition. She had moderately severe dyspnea, elevated jugular venous pressure, slightly enlarged liver and a heaving parasternal impulse. A low-pitched rumbling diastolic and presystolic murmur of grade 2/6 intensity could be heard at the apex. The electrocardiogram revealed right atrial overload as the only abnormality. On X-ray examination, the heart was only slightly enlarged, but the left atrium and right ventricle were prominent. Some roentgenograms disclosed definitely increased venous engorgement in the right upper lung field (Fig. 1).

On right heart catheterization, pulmonary hypertension (pressure 70/36 mm Hg) and increased pulmonary wedge pressure (mean 32 mm Hg) were found. Pulmonary angiography revealed a constant filling defect in the left atrium.

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Serum protein studies revealed a reduced albumin/globulin ratio. These findings led to the diagnosis of left atrial myxoma with obstruction of the mitral orifice, systemic reaction and probable cerebral embolism 14 years earlier.

At operation, performed with cardiopulmonary bypass, cardiac arrest occurred before the start of the perfusion. Heart massage and direct current electric shock were applied successfully and the operation was continued. Right atriotomy exposed a myxoma attached by a slender stalk to the rim of the fossa ovalis; the preparation weighed 7 g. When this tumor was resected with a portion of the interatrial septum, a large pedunculated myxoma (39 g) was seen in the left atrial cavity. This tumor was also excised and a tumor embolus removed from the left femoral artery. The patient died on the 1st postoperative day without regaining consciousness. At necropsy, multiple tumor emboli in several organs were found.

Case 2: T.T.K., son of A.E.K., was born in 1956. During the winter of 1968, although previously healthy, he felt temporary numbness in the lower limbs and a slight cramp in the calf after leg exercise. In March 1968 he experienced sudden intense pain in the left leg, which became cold and painful; no arterial pulsation could be felt. An operation was performed at the local hospital and a large embolus consisting of loose myxomatous tissue was removed from the left femoral artery as were smaller similar emboli from the left popliteal artery and its branches. The following day two toes on the right foot became blue and painful, and a rise in the serum creatinine level suggested renal involvement. The erythrocyte sedimentation rate was accelerated and serum electrophoresis revealed a reduced albumin/globulin ratio. Histologic examination confirmed the suspicion of cardiac myxoma, and the patient was sent to the University Central Hospital in Helsinki for heart surgery.

On physical examination, the auscultatory findings were normal. The electrocardiogram revealed signs of mild left atrial overload. On X-ray examination the heart was slightly enlarged and the left atrium and the right ventricle were prominent. Right heart catheterization revealed normal findings. Pulmonary angiography disclosed a large filling defect that moved from the left atrium to the left ventricle during each diastole.

Open heart surgery was performed 4 days after admission and a left atrial myxoma weighing 35 g was resected. The postoperative course was uneventful. Later the two toes of the right foot had to be amputated and the left leg needed skin transplantation. The boy returned to school 3 months after the operation and he is at present asymptomatic except for slight stiffness of the left ankle. Chromosomal analysis revealed a normal karyotype.

Case 3: A.A.K., the eldest son of A.E.K., was born in 1949. At age 16 years, he had an acute disease with fever, cough and pain in the left axilla; the erythrocyte sedimentation rate was more than 100 mm in 1 hour. He was admitted to the local hospital, where a roentgenogram revealed a small amount of fluid in the left pleural cavity. The electrocardiogram was initially normal but within a few weeks showed T wave inversions and increased R wave amplitude in the right precordial leads. A loud gallop was intermittently audible. A faint transient diastolic murmur later aroused suspicion of mitral stenosis. The patient also had recurrent attacks of unconsciousness. Serum electrophoresis revealed increased alpha 2, beta and gammaglobulins and a reduced albumin/globulin ratio. Because acid-fast bacilli were detected with use of gastric lavage, antituberculous therapy was started. The symptoms, including the high erythrocyte sedimentation rate, disappeared within 3 months.

During the following 2 years the patient had progressive fatigue and palpitations. A loud midsystolic murmur due to

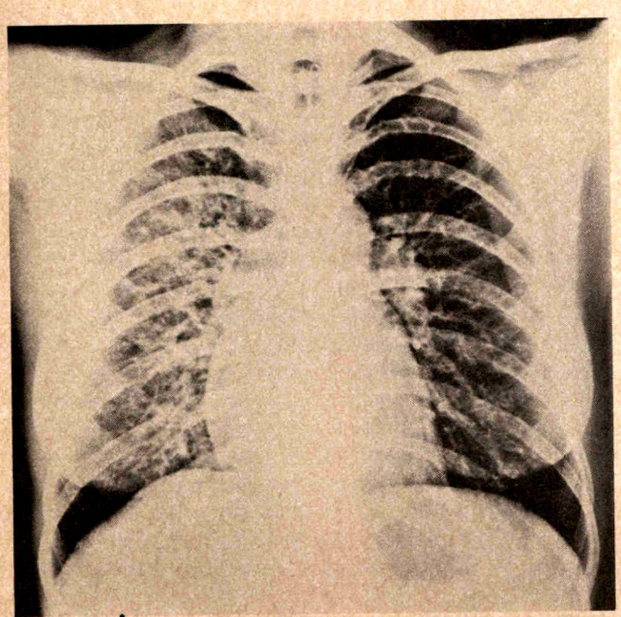

FIGURE 1. Case 1. Chest roentgenogram documenting the transient disparity of pulmonary venous engorgement due to left atrial myxoma.

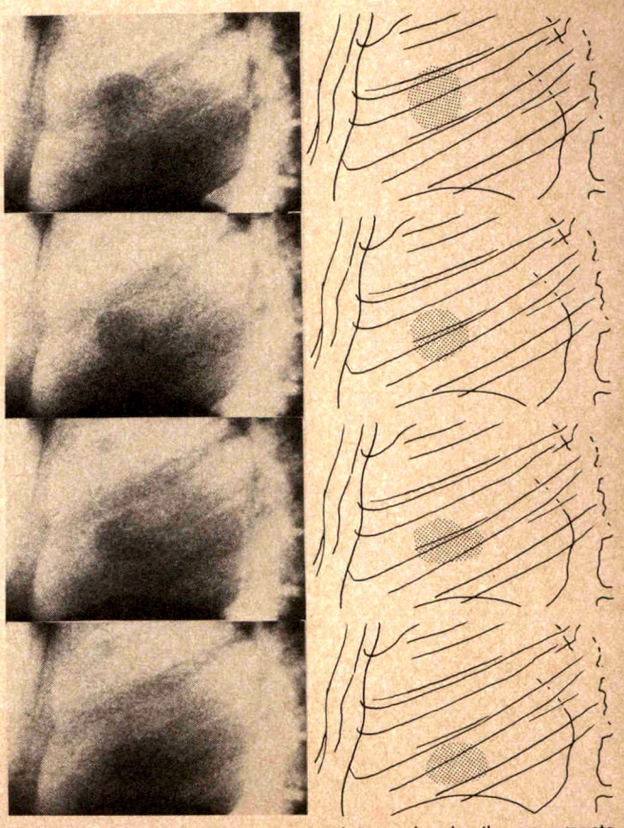

FIGURE 2. Case 3. Cinefluoroscopic pictures showing the movements of the calcified atrial myxoma from the right atrium to the right ventricle.

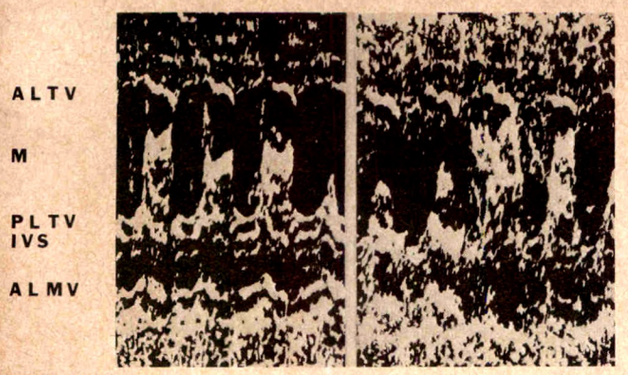

FIGURE 3. Case 3. Echocardiogram revealing a dense tumor moving into the large tricuspid orifice and enlarged right ventricular cavity during diastole, recorded in two slightly different projections. ALMV = anterior leaflet of mitral valve; ALTV, PLTV = anterior and posterior leaflet of tricuspid valve, respectively; IVS = interventricular septum; M = myxoma.

tricuspid regurgitation was now audible at the mid-sternum. When his younger brother was operated on for cardiac myxoma, suspicion arose that the patient's symptoms could be due to the same condition.

On admission to the University Central Hospital in Helsinki, physical examination revealed elevated jugular venous pressure with a systolic venous pulse, strong left parasternal impulse and a typical grade 3/6 tricuspid systolic murmur accompanied intermittently by a tricuspid inflow murmur and a loud third sound gallop. The electrocardiogram revealed right and left atrial and right ventricular overload. The heart was moderately enlarged on X-ray examination, and the right atrium and ventricle were prominent. On fluoroscopy a calcified tumor was seen moving between the right atrium and ventricle (Fig. 2). Echocardiography revealed a dense mass filling the large tricuspid orifice and enlarged right ventricular cavity during diastole (Fig. 3). As a safety precaution, right heart catheterization studies were limited to pressure measurements in the right atrium, where a completely ventricularized curve with a mean pressure of 10 mm Hg was found. Injection of contrast medium into the superior vena cava visualized a filling defect in the right atrial cavity.

Operation was performed under circulatory bypass and a calcified myxoma the size of a pingpong ball (about 30 g) was found in the right atrium. It was attached to the rim of the fossa ovalis by a pedicle 0.5 by 1 cm thick and swung freely to and fro in the tricuspid ostium. The septal and posterior cusps of the valve were destroyed. The tumor was removed together with a flap of the septum. The remnants of the tricuspid valve were resected and replaced with a Cutter-Smeloff valve.

Postoperatively, the patient had complete atrioventricular block and was unconscious for a week. A permanent pacemaker was implanted. He gradually recovered and is now almost free from cardiac and neurologic symptoms. Chromosomal analysis revealed a normal karyotype.

Case 4: A.J.K., son of A.E.K., was born in 1955. At age 10 years bronchiectasis of the left lung was found. The erythrocyte sedimentation rate was continuously slightly elevated and this finding was attributed to the lung disease. In 1968, when his younger brother (Case 2) was operated on for cardiac myxoma, the patient was also referred for examination. Right heart catheterization and pulmonary angiography revealed normal findings. On follow-up there was a gradual rise in the erythrocyte sedimentation rate and increase in the right ventricular forces in the electrocardiogram. In November 1973 the patient was sent to the University Central Hospital in Helsinki for surgical treatment of the bronchiectasiae. During the train journey a right-sided hemiplegia with aphasia suddenly developed.

On admission, grade 2/6 low pitched diastolic and presystolic murmurs were heard at the apex, and a left parasternal impulse was felt. The heart size on X-ray examination was normal with slight prominence of the left atrium and right ventricle. Right heart catheterization revealed normal findings. Pulmonary angiography disclosed a filling defect in the left atrium and, after injection of contrast medium into the superior vena cava, a filling defect in the right atrium was suspected. On echocardiography a left atrial tumor was visible but the right atrium and ventricle were normal. The erythrocyte sedimentation rate was 49 mm in 1 hour and the serum albumin/globulin ratio was reduced.

During open heart surgery, the right atrium was found to be free of tumor tissue, but a myxoma weighing 25 g was resected from the left atrium. The postoperative course was uneventful. The neurologic symptoms have gradually decreased, and the patient is now fully active.

Discussion

Clinical Features

The clinical findings in these cases were generally the same as those described in several case reports and reviews.[8–11] The course of the disease was variable and often confusing. Some special clinical features shall be mentioned.

Embolization: If the myxoma is biatrial, the disease has a more malignant course, and both systemic and pulmonary embolization can occur.[12–14] In the mother (Case 1), the severe systemic reactions were proportional to the large amount of tumor tissue. However, there was no evidence of embolism before the final massive embolization occurred during the resuscitation procedure. This finding might be interpreted as evidence for the hypothesis that the systemic signs are autoimmune reactions to the tumor tissue or due to necrosis of the myxoma.[15–17] The accelerated erythrocyte sedimentation rate has also been regarded as a consequence of embolization.[9] In effect, Patient 3 had a high erythrocyte sedimentation rate at the time of the pulmonary disease, probably as a result of embolization, and a normal sedimentation rate preoperatively at the time when tricuspid regurgitation due to valve destruction had occurred. Thus, there is evidence suggesting that both mechanisms may be involved in the genesis of the systemic reactions.

Syncope: Before operation Patient 3 had syncopal attacks, which did not recur postoperatively. In a previously reported case of right atrial myxoma with similar symptoms,[18] no evidence of peripheral embolization was found at autopsy and the cause of the attacks remained obscure. There is experimental evidence[19] that even large tumors can pass freely from the left atrium to the left ventricle without causing obstruction. Because the tricuspid valve ostium is normally larger than the mitral valve ostium, it is not probable that the syncopal attacks could have been caused by temporary obstruction of inflow through the tricuspid ostium. In Case 3 the movements of the calcified myxoma were visible on fluoroscopy—a phenomenon earlier described in cases

of right[20–22] and even left[8,23] atrial myxoma. The swinging of the tumor had led to destruction of the tricuspid valve. Severe valve destruction caused by the movements of the tumor has been reported only in cases of right atrial myxoma.[22,24,25] The damage may extend also to the subendocardial conductive tissue; in fact, there is evidence that fibrous thickening can occur in the right ventricular endocardium beneath the septal cusp of the tricuspid valve.[26] This could explain the postoperative atrioventricular dissociation in Case 3, since surgical trauma to the conductive tissue seemed improbable in this case.

Pulmonary venous engorgement: In addition to other radiologic findings, periodic disparity in the pulmonary venous engorgement is a useful sign;[27] it was found in 2 of 14 consecutive roentgenograms in our Case 1. Thus, frequent roentgenograms are needed to detect this sign in cases of suspected left atrial myxoma.

Diagnostic Methods

Echocardiography has proved a useful diagnostic tool in left atrial myxoma.[28] It is considered less useful when the myxoma is right atrial, and only one case of echocardiographic diagnosis of this condition has been reported.[29] In our Cases 3 and 4 (Fig. 3), echocardiographic studies with either a positive or a negative result were reliable.

Interesting information on the rate of growth of the tumor was gained in Case 4, where pulmonary angiograph was normal 5 years before the left atrial tumor was visualized in a new examination. One previous report[30] described recurrence of a myxoma 17 months after its complete removal. In another,[7] pulmonary angiograms were normal 2 years before the tumor was diagnosed. In cases in which cardiac myxoma is suspected but angiograms are normal, echocardiography is probably the best means for follow-up examination. In some cases repeated angiography may be necessary.

Pathogenesis

The pathogenesis of cardiac myxoma is poorly understood. It is now considered to be a true neoplasm[31] that is almost always benign histologically. It has been found in patients aged 3 months to 95 years and in both sexes. However, most patients are aged 30 to 50 years, and incidence is greater in women with a sex ratio of 3:1.[32,33] Most of the cardiac myxomas are atrial, left-sided tumors being three times more common than right-sided tumors. The tumor is supposed to originate from the cell remnants near the foramen ovale,[34,35] where the potential for tissue proliferation is physiologically preserved to the neonatal period and even into adult life. It is possible that a disturbance of the fetal development in this area could form a basis for later myxomatous growth.

In three of our four patients minor malformations in different organs were also found (double ureter, spondylolisthesis and radiologic evidence for cystic fibromas of tibia and femur, each in a different patient). No conclusions can be drawn from this finding although in a previously reported case[36] radiologic findings of similar bone lesions were found.

Genetic Transmission

Environmental factors could explain the familial occurrence of the disease (for example, an infection common to the affected family members). In fact, evidence of a viral origin of cardiac myxoma has been suggested in a recent report.[37] In our cases, however, the time relations of the initiation of the disease in the different patients argue against the hypothesis of an

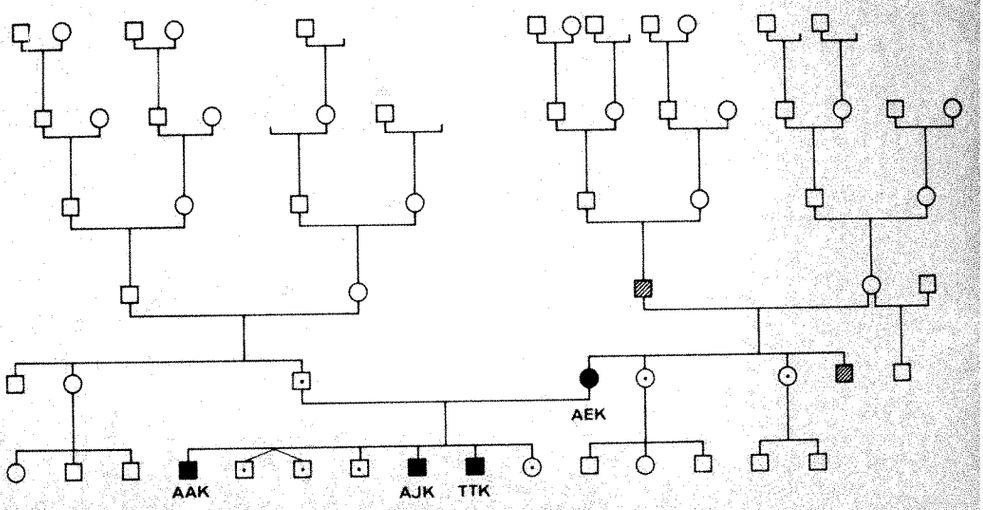

FIGURE 4. Pedigree showing the patients, their close relatives and the traced ancestors. AEK = Case 1; TTK = Case 2; AAK = Case 3; AJK = Case 4.

□ no clinical examination
■ cardiac myxoma verified
▨ died with symptoms consistent with cardiac myxoma; diagnosis uncertain
⊡ examined by the authors; no evidence of cardiac myxoma

infectious origin. The most probable explanation for the familial occurrence of cardiac myxoma is genetic transmission. Previously cardiac myxoma has twice been described in siblings.[6,7] No other family data were given and the mode of transmission was not discussed. Additionally, a family has been reported in which the 18 year old son had left atrial myxoma and lentiginosis, and the mother, "heavily freckled," had died of "heart disease in her mid-forties." [38]

If atrial myxoma were due to a single gene, it would frequently have a familial occurrence. Yet the family described is only the third reported such agglomeration. Until recently, however, the correct diagnosis of cardiac myxoma in a living patient has been exceptional, and no active steps have been taken to find other cases among the relatives. Affected persons may also die or have severe symptoms before having children, which may reduce the familial occurrence in dominant transmission.

In this family, cardiac myxomas occurred in two successive generations, namely, in a mother and three of her sons. This is strongly suggestive of dominant transmission. An autosomal recessive mode of inheritance with pseudodominant appearance is not entirely excluded, especially because the majority of the ancestors came from the same sparsely populated area in Finland. In such conditions even rare recessive genes might well be possessed by parents of more than one sibship. The ancestors of the affected siblings were traced back four generations without finding common ancestors for the parents and the husband of the affected mother (Fig. 4). Thus, these persons were not third cousins or more closely related. Sex-linked recessive inheritance is excluded because a female member was affected.

The father and a brother of the affected mother died from an unidentified disease of short duration at the age of 46 and 23 years, respectively. The causes of death remain unknown, but there were some features consistent with the clinical findings of myxoma. If these relatives had also had myxoma, it would confirm the hypothesis of autosomal dominant transmission in this family. This possibility should be taken into account by those investigating patients with cardiac myxoma.

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Surgical Treatment of Congenital Unilateral Pulmonary Arterial Stenosis With Contralateral Pulmonary Hypertension

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This report describes the diagnosis and surgical treatment of a 48 year old patient with congenital right pulmonary arterial ostial stenosis, no intra- or extracardiac shunts and systemic levels of pressure in the main and left pulmonary artery with pulmonary vascular obstruction in the left lung.

Operation consisted of a bypass graft of 10 mm woven Dacron from the main pulmonary artery to the distal right pulmonary artery producing an immediate 50 percent reduction in mean left pulmonary arterial pressure. Late postoperative evaluation revealed equal perfusion of both lungs, maintenance of the reduced pulmonary arterial pressure and improvement from New York Heart Association functional class IV to class I.

Congenital stenosis of the origin of one or both principal branches of the pulmonary arterial system has been reported only infrequently and is usually accompanied by other malformations of the heart and great vessels.[1–6] The patient to be described demonstrated congenital stenosis of the origin of the right pulmonary artery with severe pulmonary hypertension and pulmonary vascular obstruction in the left lung and underwent successful surgical treatment of this unusual lesion.

Case Report

A 48 year old woman was admitted to her local hospital for severe dyspnea that had progressed in the preceding five years. During the previous year, her condition had deteriorated until she was bedridden and in New York Heart Association functional class IV.

Her previous medical history was essentially normal and she had no previous hospitalizations except for childbirth. She had been told she had a heart murmur when she was a child but there was no history of rheumatic fever or thrombophlebitis. She had a been a heavy cigarette smoker.

Physical examination disclosed moderate cyanosis and clubbing of the fingernails. The lungs were clear. The jugular venous pressure was increased and there was a marked right ventricular impulse. The first heart sound was normal and was followed by an ejection click, the latter initiating a grade 2/6 systolic ejection murmur in the pulmonary area. The second heart sound was narrowly split and the pulmonary component was markedly accentuated. The blood pressure was 140/90 mm Hg, all peripheral arterial pulsations were within normal limits and there was no evidence of thrombophlebitis.

Chest roentgenogram and fluoroscopy revealed that the heart was slightly enlarged with right ventricular prominence. The main left pulmonary artery was greatly enlarged but the right pulmonary artery could not be identified. The pulmonary vascular pattern was increased on the left and markedly decreased on the right (Fig. 1). The hemoglobin was 15.2 g and hematocrit 45 percent; the systemic arterial oxygen tension was 48 mm Hg and the oxygen saturation 89 percent. The electrocardiogram disclosed sinus rhythm, incomplete right bundle branch block and right ventricular and right atrial hypertrophy.

The patient was referred to the Peter Bent Brigham Hospital where findings on physical examination were unchanged. A xenon-133 ventilation-perfusion lung scan (Fig. 2A) disclosed severely reduced perfusion of the right lung with normal perfusion of the left lung.

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Right heart catheterization and pulmonary arterial angiography were performed. The main and left pulmonary arterial pressures were 160/60 mm Hg (mean 125), the right pulmonary artery could not be entered, the right ventricular pressure was 160/6 and the right atrial pressure 6 mm Hg. The pulmonary arterial angiogram demonstrated a 95 percent stenosis of the right branch at its takeoff from the main pulmonary artery (Fig. 3A). Flow through the small right pulmonary artery to the right lung was severely reduced, but an appropriate number of peripheral pulmonary vessels in the right lung parenchyma was seen.

Surgical treatment: Operation was advised to decompress the severe left-sided pulmonary arterial hypertension and reestablish flow to the right-sided pulmonary circulation. Operative findings were massively enlarged main and left pulmonary arteries, severe right ventricular hypertrophy and a soft, thin-walled but normal-sized right pulmonary artery without intraluminal masses or thrills. After institution of total cardiopulmonary bypass, the aorta was retracted medially and the superior vena cava laterally to facilitate complete dissection of the right pulmonary artery beyond the first lobar branch. Before bypass, pressure in the distal right pulmonary artery was 20/15 mm Hg (mean 18) (Table I). Blood flow in the right pulmonary artery appeared to be entirely retrograde from the bronchial circulation.

A main pulmonary artery-right pulmonary artery bypass was then accomplished with a 10 mm woven Dacron® graft. The distal end to side anastomosis to the right pulmonary artery was performed first using running 5–0 Prolene®; the graft was brought anterior to the aorta and anastomosed end to side to the dilated main pulmonary artery. Biopsy of the main pulmonary arterial wall demonstrated marked thickening and atherosclerotic changes in the intima and media.

The patient was weaned off cardiopulmonary bypass without difficulty. Pressure measurements (Table I) off cardiopulmonary bypass showed an immediate decrease in the main pulmonary arterial pressure and a 10 mm Hg pressure stepdown from the main to the right pulmonary artery. Right and left lung biopsies were performed after the heparin was neutralized; the left lung showed hypertensive pulmonary

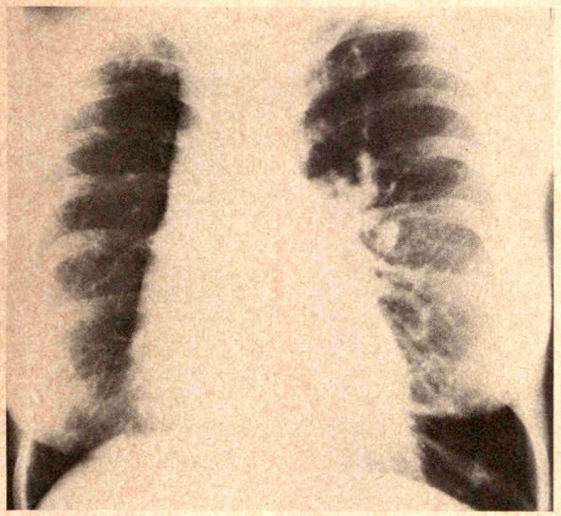

FIGURE 1. Posteroanterior chest roentgenogram. Note the oligemia of the right lung.

TABLE I

Pulmonary and Systemic Arterial Pressure Measurements (mm Hg) Before and After Main to Right Pulmonary Artery Bypass Graft

	Brachial Artery	Main Pulmonary Artery	Right Pulmonary Artery
Preoperative	160/130 (140)	160/60 (90)	. . .
Before cardiopulmonary bypass	120/80 (90)	120/50 (70)	20/15 (18)
1 hour after cardiopulmonary bypass	110/80 (75)	60/40 (55)	50/35 (40)
5 days postoperatively	120/70 (80)	60/35 (40)	. . .
8 months postoperatively	130/70 (85)	50/20 (35)	. . .

Figures in parentheses indicate mean pressures.

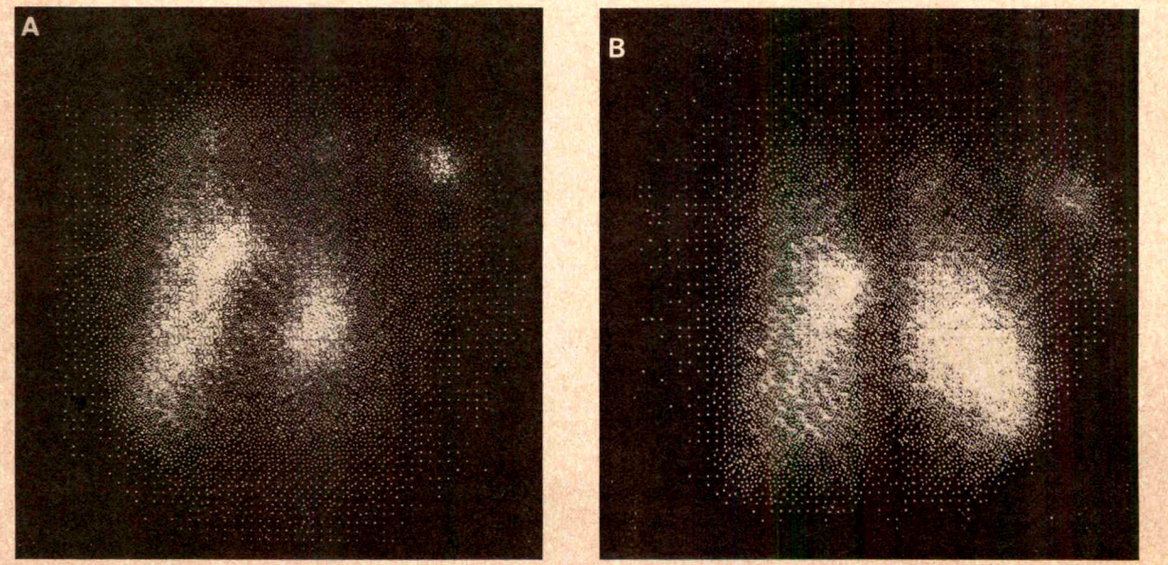

FIGURE 2. Xenon-133 ventilation-perfusion posterior lung scans. **A,** preoperative. There is only faint opacification of the right lung. **B,** postoperative. There is equal opacification of the right and left lungs.

vascular disease whereas the right pulmonary arterioles were normal (Fig. 4).

Postoperative course: Endotracheal intubation was maintained until the 3rd postoperative day because of a persistent reduction in arterial saturation that gradually increased with positive pressure respiration and diuretic therapy. Pressure in the main pulmonary artery on the fifth postoperative day was 50 percent of the simultaneously measured systemic pressure (Table I).

The patient was discharged on her 14th postoperative day and did well in the follow-up period of 8 months. She noted relief of cyanosis and considerably more energy so that she was now in functional class I. A postoperative ventilation-perfusion scan showed equal perfusion of both lungs (Fig. 2B). Recatheterization 8 months postoperatively revealed that pressure was 50/2 mm Hg (mean 35) in the main pulmonary artery, 50/4 in the right ventricle and 4 (mean) in the right atrium; systemic pressure was 130/70 mm Hg (mean 85). Angiography demonstrated the patent prosthetic bypass graft from the main to the right pulmonary artery with excellent runoff in the right pulmonary vasculature (Fig. 3B).

Discussion

Congenital stenosis of the peripheral branches of the pulmonary arterial tree has generally been associated with intracardiac shunts, the tetralogy of Fallot, and other congenital malformations.[2–8] Less common is the syndrome of multiple peripheral pulmonary arterial stenosis[9] and only rarely described is stenosis of the right or left main pulmonary artery without associated abnormalities.[7]

Peripheral pulmonary arterial stenosis was first described pathologically by Oppenheimer[10] in 1938 and clinically by Moeller[11] in 1953 after angiography became available. This is an unusual condition; Delaney and Nadas[12] found only 4 patients with this diagnosis in 3,250 patients undergoing right heart catheterization, whereas Weinberg et al.[4] found only 39 in 2,000 such patients.

Incidence of contralateral pulmonary hypertension: In our patient, the contralateral (left) lung

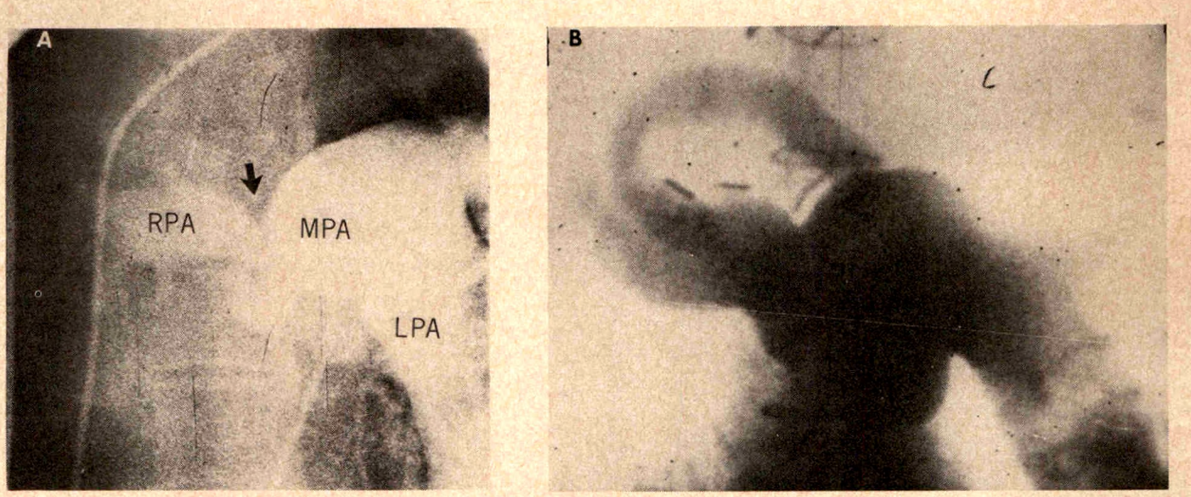

FIGURE 3. Pulmonary arterial angiograms. **A,** preoperative. There is massive dilatation of the main (MPA) and left (LPA) pulmonary arteries and 95 percent stenosis at the origin of the right pulmonary artery (RPA). **B,** postoperative. There is a patent graft from the main to the distal right pulmonary artery with perfusion of the right lung.

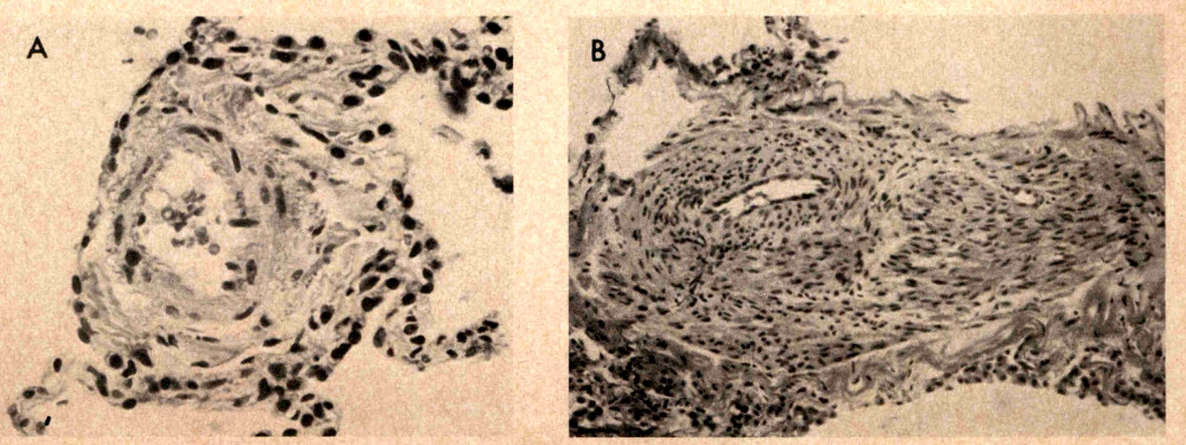

FIGURE 4. Photomicrographs of lung biopsy specimen. **A,** right lung, showing a normal pulmonary arteriole. **B,** left lung, showing medial hypertrophy of a pulmonary arteriole. (Hematoxylin/eosin × 400 [**A**] and × 100 [**B**], reduced by 49 percent.)

received virtually the entire right ventricular output, resulting in pulmonary vascular obstructive disease of the left lung and severe hypertension in the main and left pulmonary arteries. This is an unusual finding since patients after pneumonectomy usually tolerate the total right ventricular output into one lung. Experimental and clinical observations by Vogel et al.[13] showed that ligation of the right pulmonary artery in calves at sea level or at 5,200 feet (1,560 meters) above sea level led to severe pulmonary hypertensive changes in the left lung, but the reverse did not occur when the left pulmonary artery was ligated.[12] Observations in patients with agenesis of a major pulmonary artery are consistent with these findings. Severe pulmonary hypertension in the left lung and death occur within the 1st year of life in one third of patients who have no right pulmonary artery,[14] but absence of the left pulmonary artery does not seem to result in pulmonary hypertension in the right pulmonary artery.[14] The reported experimental and clinical observations and the clinical data in our patient probably relate to the larger volume of the right lung (55 percent) versus the left lung (45 percent)[15] so that the left pulmonary vascular volume has less capacity.

Hartmann et al.[16] found no significant increase in contralateral pulmonary arterial pressure in children with peripheral pulmonary stenosis followed up for 4 to 7 years; however, no child in their study was more than 12 years of age and the follow-up period was relatively short. Hartmann et al. suggested that since the condition appeared to be benign, surgical treatment was probably not indicated. The data in our patient, who presented at age 48 years, and the experimental and clinical observations of Pool et al.[14] suggest otherwise. The severe vascular obstructive changes in our patient were similar to the changes seen in patients with long-standing atrial septal defect.[17]

Surgical treatment: The surgical treatment of peripheral pulmonary arterial stenosis depends on the site and number of stenoses. Stenosis may occur at the supravalvular level, at the pulmonary arterial bifurcation in either the main left or main right pulmonary artery, as in our patient, or in multiple peripheral branches.[7] Single branch stenosis has been treated in patients with tetralogy of Fallot by dilatation[6] or caval-pulmonary anastomosis,[8] and multiple peripheral stenosis by saphenous vein patch angioplasties.[8,9] One previous report[1] describes an adult patient with right pulmonary arterial stenosis and agenesis of the left pulmonary artery treated with a Teflon® bypass graft from the main pulmonary artery to the distal right pulmonary artery. The technique used was similar to that used in our patient. This patient later had pulmonary hypertension in the right lung. A synthetic graft bypass for this central obstruction offers an advantage over angioplasty, but angioplasty is the most appropriate technique for correction of multiple peripheral stenoses.

This use of main pulmonary artery to right pulmonary artery bypass to relieve severe pulmonary hypertension in a patient with unilateral major pulmonary arterial stenosis and contralateral pulmonary arterial hypertension is apparently unique. Whether pulmonary hypertension will appear in the reperfused lung is uncertain although the maintenance of the low although not normal level of pressure in the main pulmonary artery, documented by cardiac catheterization studies 8 months postoperatively, and the excellent runoff in the right lung are encouraging.

Acknowledgment

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Masked Abnormal Drainage of the Inferior Vena Cava Into the Left Atrium

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A 6 year old boy with a large atrial septal defect, partial anomalous pulmonary venous drainage and unrecognized anomalous insertion of the inferior vena cava into the left atrium had cyanosis after closure of the atrial defect. Repeat study revealed direct drainage of the inferior vena cava into the left atrium with moderate arterial oxygen desaturation. At repeat operation an unusual positioning of the inferior vena cava was seen. After reopening of the atrial defect, the pulmonary venous and systemic venous drainage anomalies were identified. A Dacron patch was inserted so as to divert flow to the proper atrium. Repeat catheterization 3 months after operation revealed a normal heart with no obstruction; arterial oxygen saturation was normal. The child has continued to do well 3 years after operation.

Abnormal drainage of the inferior vena cava into the left atrium may occur rarely as an isolated congenital anomaly,[1–4] be associated with an atrial septal defect[5,6] or be seen with other venous drainage abnormalities.[7] More often, it is a complication of operative repair of a large secundum atrial septal defect.[8–12] We describe here a 6 year old boy with an atrial defect that masked the abnormal drainage of the inferior vena cava into the left atrium. Not until after repair of the defect was the anomalous inferior vena caval drainage appreciated, diagnosed and finally rerouted.

Case Report

The patient, a white boy born on June 22, 1965, was first noted to have a heart murmur at age 3 weeks. Transient cyanosis was noted in infancy during feeding and crying, but growth and development were normal. At age 21 months, while experiencing an upper respiratory infection, the child had an episode of generalized cyanosis that lasted several hours. He was subsequently admitted to another hospital for cardiac catheterization. Physical examination at that time revealed no cyanosis or clubbing. A right ventricular impulse was present at the lower left sternal border. A systolic thrill and a grade 4/6 systolic ejection murmur were noted at the pulmonary area. The second heart sound was accentuated. The hematocrit was 42 percent. The chest roentgenogram revealed generalized cardiac enlargement with increased pulmonary vascularity. The electrocardiogram revealed a mean QRS axis of +150° with tall R waves in the right precordial leads consistent with right ventricular hypertrophy.

At cardiac catheterization, the venous catheter from the leg was thought to enter the left atrium through an atrial septal defect. Oximetry disclosed a significant increase in oxygen saturation at the atrial level with an arterial saturation of 99 percent (Table IA). Right ventricular systolic pressure was approximately half of the systemic level. Cineangiography performed in the left atrium disclosed a left to right shunt at the atrial level.

The patient was operated on under cardiopulmonary bypass at age 28 months. The operative note records that a 3 cm secundum atrial septal defect extending down to the opening of the inferior vena cava was closed with interrupted sutures. A 1 cm sinus venosus defect was also identified and closed. No further anatomic description was available. Cyanosis was noted on the 2nd postoperative day and persisted and increased in severity. Dyspnea also became apparent after strenuous activity.

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At age 5 1/2 years, the boy was admitted for a second cardiac catheterization (Table IB). Cineangiography now revealed direct drainage of the inferior vena cava into the left atrium (Fig. 1); systemic arterial oxygen saturation was 89 percent. The patient was then referred to New York University Hospital at age 6 years for operative repair.

At the second open heart procedure, the unusual position of the inferior vena cava was readily evident. It entered the heart more than 3 cm to the left of the usual site. The inferior vena cava was cannulated directly through a stab wound in its midportion, a cannula advanced and secured with a snare. After right atriotomy, no orifice of the inferior vena cava could be seen. Two small right superior pulmonary veins entered the right atrium slightly below the superior vena caval opening. Sutures in the atrial septum from the previous operation were identified. Once the atrial septum was completely reopened, the inferior vena caval orifice was clearly seen in the left atrium. The right inferior pulmonary vein was draining slightly to the right of and superior to the inferior vena cava (Fig. 2A). Reconstruction of the atrial septum was accomplished with a knitted Dacron® patch sewn below the entry point of the inferior vena cava into the left atrium. The patch was then attached to the right atrial surface so as to direct the right pulmonary veins into the left atrium and the inferior vena cava into the right atrium (Fig. 2, B and C). At the conclusion of bypass, the oxygen saturation levels in the right atrium, right ventricle and pulmonary artery were identical and the arterial blood was fully saturated.

The postoperative course was uneventful. At repeat cardiac catheterization performed 3 months later to assess the repair (Table IC), there was no residual shunt; intracardiac pressures and arterial blood gas and oxygen saturation levels were normal. Pressure data and cineangiography revealed normal unobstructed drainage of the inferior vena cava into the right atrium and of the pulmonary veins into the left atrium (Fig. 3). Three years after the second operation, the boy continues

TABLE I

Cardiac Catheterization Data

	A. Age 2 Years (preoperative)		B. Age 5.5 Years (after 1st, before 2nd operation)		C. Age 6 Years (after 2nd operation)	
Site	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)
VC	76	...	...	...	...	...
RA	89	(7)	...	...	...	(4)
RV	...	52/8	...	...	...	22/5
PA	...	...	...	...	...	22/10(14)
FA	99	100/70	89	...	94	...
LV	...	...	...	95/10	...	...
LA	97	(7)	...	(6)	...	...
Cine angiogram	Left to right atrial shunt		IVC draining directly into LA		Normal systemic and PV drainage	

Figures in parentheses indicate mean pressures.

FA = femoral artery; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; O_2 Sat = oxygen saturation; PA = pulmonary artery; PV = pulmonary venous; RA = right atrium; RV = right ventricle; VC = venae cavae.

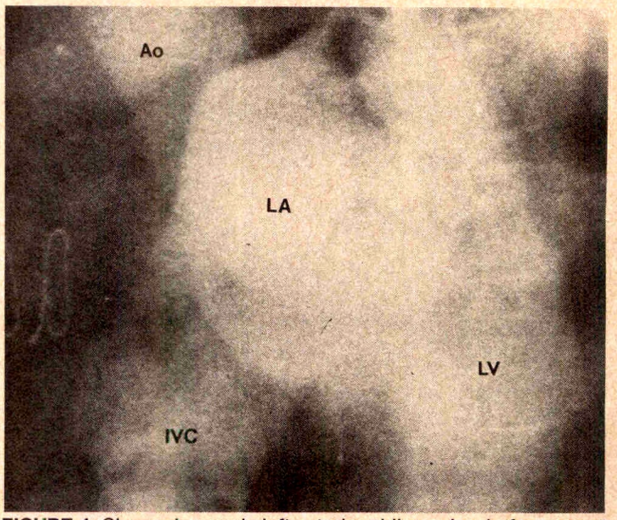

FIGURE 1. Cineangiogram in left anterior oblique view before repeat operation, showing the inferior vena cava (IVC) draining into the left atrium (LA) and subsequent filling of the left ventricle (LV) and aorta (Ao).

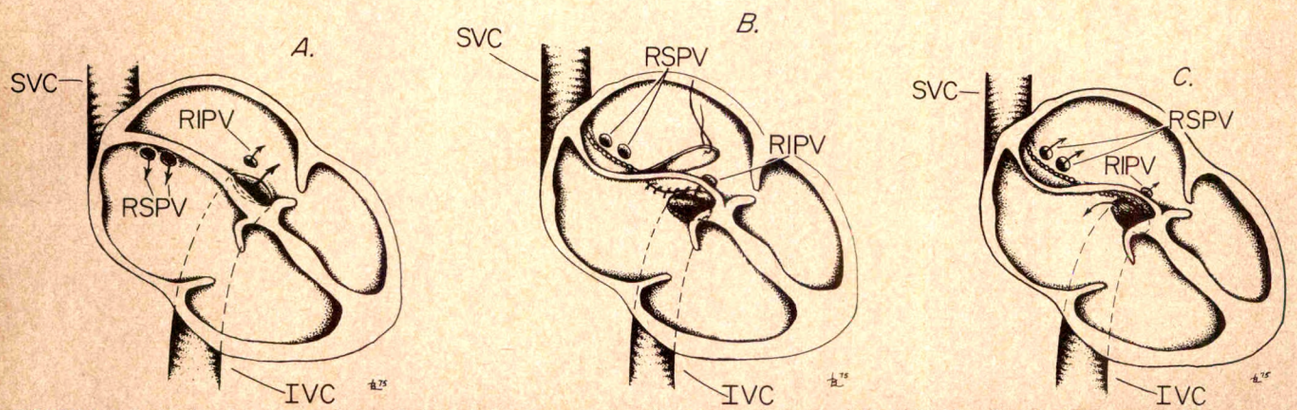

FIGURE 2. A, illustration showing the abnormal anatomy found at operation. The inferior vena cava (IVC) drained into the left atrium and the right superior pulmonary veins (RSPV) into the right atrium. The increased pulmonary blood flow resulting from the latter drainage probably minimized the cyanosis resulting from the inferior vena caval drainage into the left atrium. The left pulmonary veins (not shown) drained normally into the left atrium. RIPV = right inferior pulmonary vein; SVC = superior vena cava. **B,** surgical correction was accomplished by excising the atrial septum and inserting a Dacron patch in a sinusoidal fashion to divert the right superior pulmonary veins into the left atrium and the inferior vena cava into the right atrium. This was somewhat difficult because of the location of the inferior vena cava to the left of normal. **C,** illustration showing the final position after the Dacron patch was completed, with the inferior vena cava (IVC) entering the right atrium and both the right superior and inferior pulmonary veins entering the left atrium. RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SVC = superior vena cava.

to do well. He has no symptoms or cyanosis and he maintains normal sinus rhythm.

Discussion

There are three types of condition in which the inferior vena cava may drain predominantly into the left atrium. In the rarest type, the inferior vena cava is displaced further to the left than usual so that it empties into the left atrium and the atrial septum is intact. The anomaly may also be associated with a large low-lying atrial septal defect so that the inferior vena caval blood is diverted into the left atrium, usually as a result of a large eustachian valve. It has also been reported as a part of a complication of atrial septal defect repair, in which the atrial septum is constructed to the right of the entry of the inferior vena cava, thus accidentally diverting inferior vena caval flow into the left atrium.

Four patients with the first type of isolated anomalous drainage of the inferior vena cava to the left atrium have been described. All had cyanosis since early childhood. Gardner and Cole's patient[1] was diagnosed at autopsy at age 30 years. Three other patients described separately by Meadows[2] and Black[3] and their co-workers and Venables[4] were diagnosed after cardiac catheterization. The arterial oxygen saturation ranged from 74 to 87 percent. These patients had evidence of minimal cardiomegaly in the chest X-ray film and signs of left ventricular hypertrophy in the electrocardiogram. Heart murmurs were notably absent. Surgical repair was not undertaken in any of the surviving patients because of associated lesions (pulmonary tuberculosis, pulmonary arteriovenous fistulas and hemiplegia).

Association of anomalous drainage of the inferior vena cava with a large atrial septal defect was originally described by Rokitansky[5] in eight postmortem cases and subsequently by Gallagher et al.,[6] who described three patients with a history of cyanosis at an early age. These patients had signs and symptoms of atrial septal defect with arterial oxygen desaturation. At operation, Gallagher's patients had a large low-lying atrial septal defect with a large eustachian valve.

Iatrogenic drainage of inferior vena cava into left atrium: Inadvertent diversion of inferior vena caval flow to the left atrium during repair of an atrial septal defect has been described in operations performed with use of the hypothermic technique as well as with extracorporeal circulation. Bedford et al.[8] described this complication in 3 patients from a total of 40 whose defect was repaired with use of the hypothermic technique. Effler and Groves,[9] Staple et al.[10] and Bjork et al.[11] reported on patients with this complication whose defect was repaired with cardiopulmonary bypass. All these patients experienced cyanosis in the immediate postoperative period, and the diagnosis of incorporation of the inferior vena cava into the left atrium was confirmed at repeat cardiac catheterization. Reoperation was performed, but the morbidity and mortality were considerable. Mustard et al.[12] described similar complications in three patients after repair of an atrial septal defect, but these patients had, in addition to the defect, partial anomalous drainage of the pulmonary veins into the right atrium. These authors believe that surgical error can occur during attempts to divert an anomalously draining right lower pulmonary vein in the

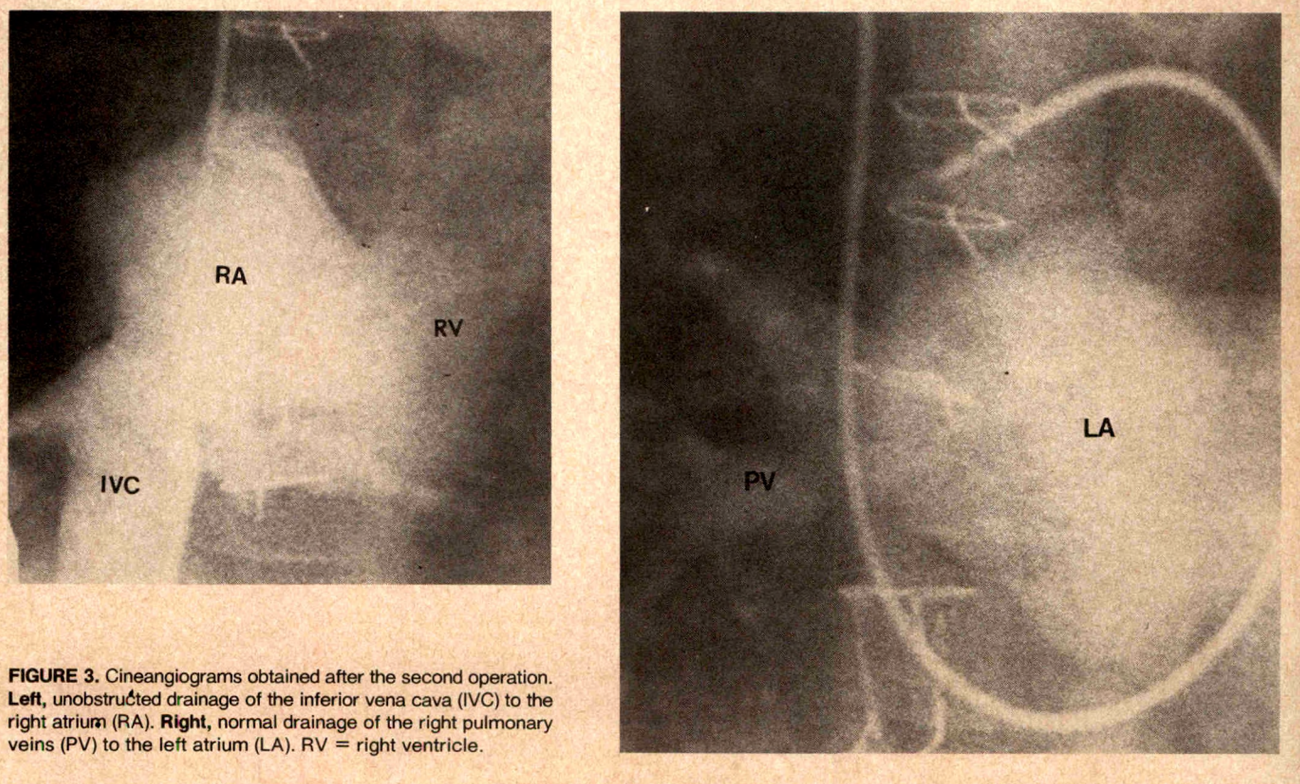

FIGURE 3. Cineangiograms obtained after the second operation. **Left,** unobstructed drainage of the inferior vena cava (IVC) to the right atrium (RA). **Right,** normal drainage of the right pulmonary veins (PV) to the left atrium (LA). RV = right ventricle.

left atrium by suturing the inferior rim of the septum to the lateral wall of the right atrium.

In our case, there was not only an associated atrial septal defect but also an inferior vena cava anatomically situated more to the left than usual (Fig. 2A). The patient had no history of cyanosis at rest but had cyanosis during infancy with crying and feeding as well as one prolonged cyanotic episode when he had a respiratory infection at age 21 months. This is not a typical history of a child with an isolated secundum defect.

Reversal of a shunt at the atrial level during changes in intrathoracic pressure and elevated pulmonary vascular resistance has been reported, but the clinical findings before the first catheterization in our case certainly favored a left to right shunt at the atrial level. The cardiac catheterization data supported this diagnosis, indicating normal arterial oxygen saturation and a large left to right shunt at the atrial level. The details from the first surgical procedure regarding cannulation of the inferior vena cava, eustachian valve size and entry site of the inferior vena cava into the atrium were not available. Two atrial defects were identified and closed by interrupted sutures, but nothing unusual was mentioned until cyanosis was observed in the recovery room. In retrospect, removal of the large pulmonary blood flow due to the atrial defect allowed the systemic saturation to reflect more accurately the anomalous drainage of the inferior vena cava. However, even this was partly masked by the partial anomalous pulmonary venous drainage that was left uncorrected.

At the second operative procedure, the anomalous pulmonary veins were recognized, as was the abnormal drainage at the inferior vena cava. It is obvious from review of published cases that incorporation of the inferior vena cava into the left atrium during repair of an atrial septal defect is a severe complication that has led to death in many cases even when the problem has been recognized and reoperation performed. The usual explanation given for this inadvertent diversion is that the eustachian valve is mistaken for the lower rim of the atrial defect and is erroneously included in the repair.

Prevention of anomalous drainage of inferior vena cava during atrial septal repair: Prevention of this error seems to depend upon awareness of the possibility of inadvertently transposing the inferior vena cava into the left atrium. Since the relation between the lower margin of the atrial septal defect and the point of entry of the inferior vena cava can vary widely, precise identification of the structures is needed before repair. Problems have usually occurred with the continuous suture technique. In some instances, initial placement of two to three interrupted sutures at the lower margin of the atrial defect will make certain that the margin of the inferior vena cava is not constricted. When identification of such landmarks is clear, facilitated by the presence of the venous cannula and inferior vena cava, it should be impossible for such a complication to occur. Our patient might have presented a further problem because anomalous pulmonary veins draining into the right atrium might obscure a portion of the operative field of the first operation. Identification of the lower margin of the atrial defect and the position of the inferior vena cava in relation to it would then be quite difficult.

Cyanosis after atrial septal repair: Cyanosis in the immediate postoperative period after open heart correction of an atrial septal defect can have many causes (low cardiac output, hypoventilation, pulmonary parenchymal disease, pulmonary vascular disease [obstructive or arteriovenous fistulas], vena caval diversion or true vena caval anomaly). Subsequent evaluation should be guided by the original location of the repaired defect. Occasionally, repeat cardiac catheterization utilizing both superior and inferior vena caval approaches will be necessary to outline the problem completely.

Anomalous drainage of the inferior vena cava into the left atrium, whether the defect is congenital or iatrogenic, is a serious one, leading to the possibility of systemic embolization. Since a large portion of the total body circulation flows through the inferior vena cava, the degree of cyanosis is usually severe and leads to polycythemia and its complications. Therefore, whenever the inferior vena caval flow enters the left atrium, either as an isolated anomaly or after operative intervention for an atrial defect, the corrective surgery should be performed as soon as possible.

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Aneurysm of the Atrial Septum in Tricuspid Atresia

Diagnosis During Life and Therapy

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Massive aneurysmal dilatation of the foramen ovale was diagnosed angiocardiographically in a patient with tricuspid atresia. The angiographic findings are distinct for this condition, and the pathogenesis appears to be related to a restrictive atrial communication in the patient with obligatory right to left shunting at atrial level. The anatomic potential for atrial restriction in the patient with tricuspid or pulmonary atresia, intact ventricular septum and diminutive right ventricle necessitates balloon atrial septostomy at the initial diagnostic cardiac catheterization. In the patient with aneurysmal dilatation of the foramen ovale, satisfactory decompression may be achieved by Blalock-Hanlon atrial septectomy, open atrial septectomy or, possibly, balloon septostomy.

A restrictive atrial communication poses a considerable hemodynamic burden to the patient with tricuspid atresia whose survival depends on an obligatory right to left shunt at this level. The pathologic findings of aneurysmal dilatation or outpouching of the atrial septum in the region of the fossa ovalis have been described by Lev[1] in a patient with tricuspid atresia and restrictive atrial communication who had a huge aneurysm of this type bulging into the left atrium and potentially obstructing the mitral valve orifice. We present herein the distinct angiocardiographic findings in a patient with tricuspid atresia and an aneurysm of the atrial septum and with a discussion of modes of therapy.

Case Report

A 2 day old male infant was referred to this institution for evaluation of cyanotic congenital heart disease. Physical examination revealed a mildly cyanosed, tachypneic infant, with a heart rate of 160 beats/min and a respiratory rate of 60/min.

Cardiac findings included a mild left ventricular impulse, a grade 2/6 systolic ejection murmur along the left sternal border and a grade 3/6 continuous ductal murmur over the pulmonary area. The second heart sound was single. All pulses were weak. The liver was palpable 3 cm below the right costal margin.

Chest radiography revealed cardiomegaly with a prominent right atrium and diminished pulmonary vascularity. There was visceral situs solitus (Fig. 1).

The electrocardiogram showed a leftward superior axis with evidence of left ventricular hypertrophy, biatrial enlargement and a low atrial or coronary sinus pacemaker (Fig. 2).

Cardiac catheterization was performed shortly after admission. The hemodynamic findings are summarized in Table I. The catheter course suggested tricuspid atresia. The left ventriculogram demonstrated a large left ventricle, high ventricular septal defect, hypoplastic right ventricular outlet chamber, moderate pulmonary stenosis and a patent ductus arteriosus. The pulmonary arteries were mildly hypoplastic. The great vessels were normally related.

A cineangiocardiogram performed at the junction of the inferior vena cava and right atrium revealed a dilated right atrium with very faint opacification of the left ventricle and ascending aorta (Fig. 3). During right atrial systole, the aneurysm bulged massively into the left atrium, almost reaching the left heart border. In right atrial diastole, the aneurysmal dilatation decreased in size. At the conclusion of the procedure a balloon septostomy was attempted but was

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not considered successful. The final anatomic diagnoses were tricuspid atresia (type Ib), pulmonary stenosis, hypoplastic right ventricle, patent ductus arteriosus and aneurysmal dilatation of the atrial septum. The systemic hypotension was attributed in part to severe restriction of obligatory atrial flow.

A Blalock-Hanlon atrial septectomy, a Waterston shunt, and ligation of the ductus arteriosus were accomplished at age 3 days. The infant tolerated the procedure well; his cyanosis lessened and heart size decreased. Sepsis due to a gram negative organism developed and he died 3 days postoperatively. A necropsy examination was not performed.

Discussion

Malformations of the septum primum component of the interatrial septum have been characterized by partial or total absence, fenestration, neoplasia, premature closure and relative malposition.[2–4] In certain congenital cardiac anomalies right to left shunting at the atrial level is obligatory. In patients with tricuspid atresia, the interatrial communication represents the only exit from the blind right atrium. Likewise, although the right atrium in the patient with pulmonary atresia and intact ventricular septum may decompress through the sinusoidal-coronary arterial communications, an atrial communication is almost invariably present.

The clinical features of atrial restriction in the patient with tricuspid atresia have previously been described.[5] Anatomically, the restriction is manifested by an obliquely patent foramen ovale or several fenestrations in the septum primum with the septum primum bulging into the left atrium. Massive aneurysmal dilatation of the septum primum as manifested in our case is undoubtedly rare. This grotesque dilatation is probably evidence of severe restriction but might represent an associated anomaly. Thompson et al.[6] have described an adult with a filling defect in the right atrium, thought to be caused by a tumor, probably a myxoma. At surgery the defect was found to be due to a redundant and fibrous interatrial septum. Other examples of aneurysmal sacculation of the atrial appendage in patients without congenital heart disease have been described.[7–11] In addition, Rowe et al.[12] have described an infant with recurrent tachyarrhythmias and multiple saccular aneurysms of the right atrium. It is remotely possible that these two conditions are related.

Decompression of the restrictive atrial communication can be achieved with balloon atrial septostomy,

TABLE I

Cardiac Catheterization Data

Site	Oxygen Saturation* (%)	Pressure (mm Hg)
Inferior vena cava	60	. . .
Superior vena cava	59	. . .
Right atrium	60	*a* 11; *v* 5; m 5
Left atrium	72	*a* 11; *v* 5; m 5
Left ventricle	80	42/11
Aorta	80	42/20
Pulmonary artery	Not entered	. . .

*All saturation data were obtained while the infant was breathing 100 percent oxygen.
a = *a* wave; m = mean; *v* = *v* wave.

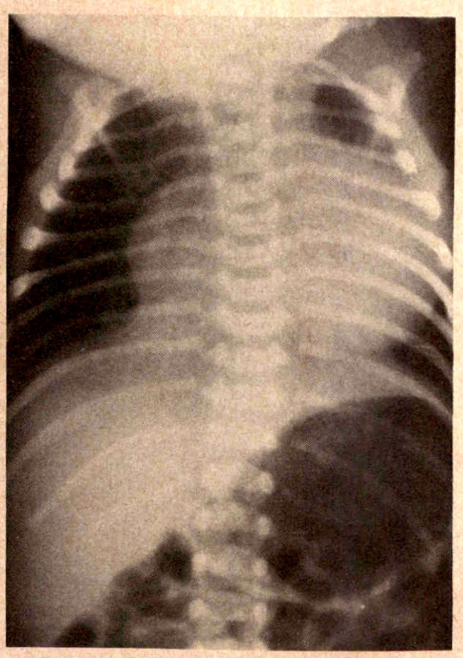

FIGURE 1 (top). Chest radiograph.

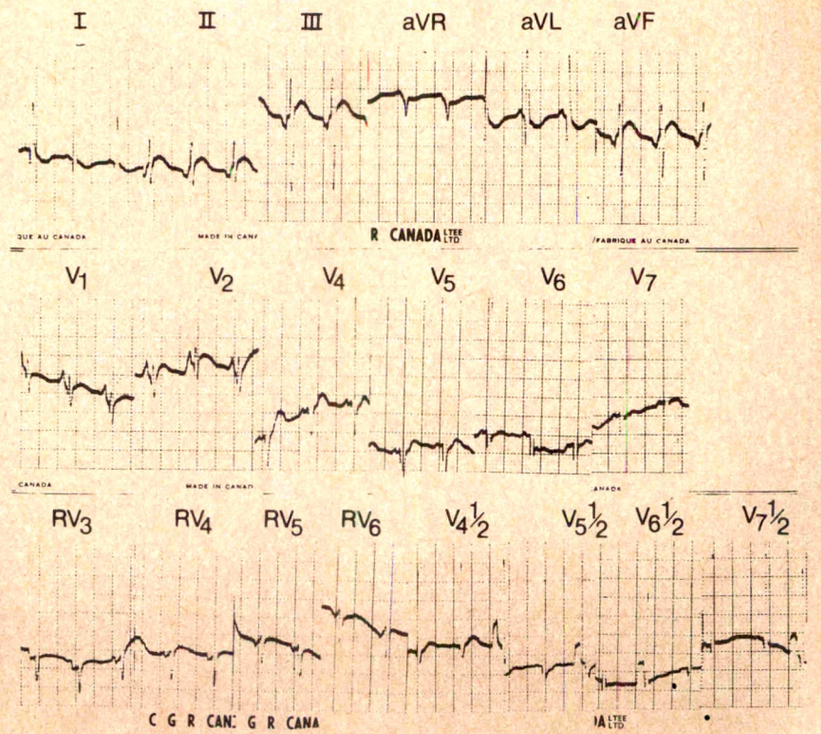

FIGURE 2 (right). Electrocardiogram.

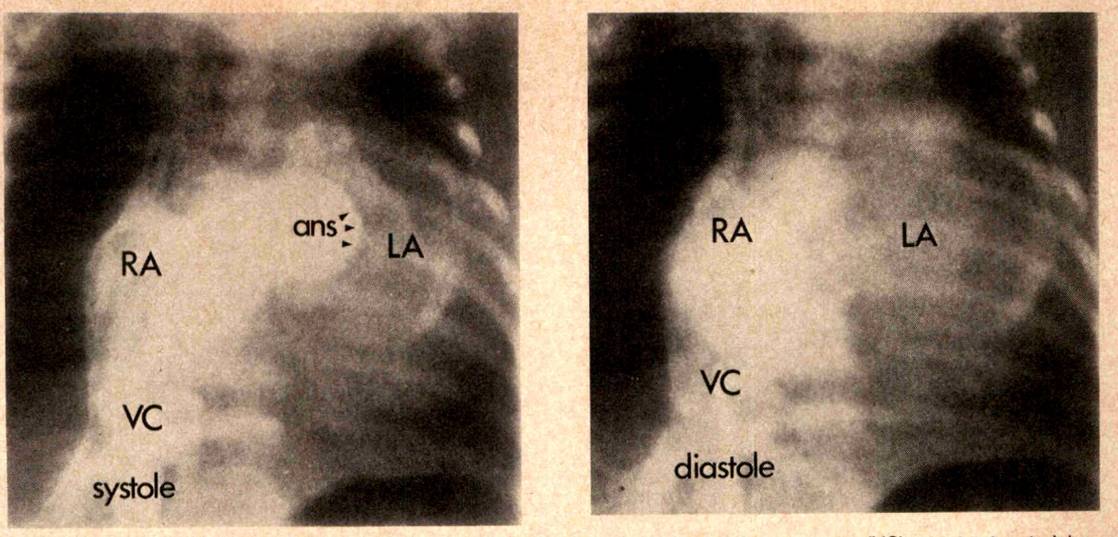

FIGURE 3. Cineangiocardiograms. **Left,** during right atrial systole. With the catheter in the inferior vena cava (VC), contrast material opacifies the vena cava, hepatic veins and right atrium (RA). The massive aneurysmal dilatation of the foramen ovale (ans) is well-visualized during right atrial systole. Opacification of the left atrium (LA) is noted. The sequence of opacification is typical for tricuspid atresia. **Right,** during right atrial diastole and filling, the aneurysmally dilated foramen ovale is not evident. The left heart chambers are never densely opacified, probably because of severe atrial restriction. Between atrial systole and diastole, a "ping-pong" ball effect is produced by the phasic aneurysmal dilatation of the foramen ovale.

the Blalock-Hanlon atrial septectomy or open atrial septectomy using hypothermia or inflow occlusion. The incidence of true secundum atrial defects in patients with tricuspid atresia or pulmonary atresia and intact septum is not known. Because atrial restriction can mitigate successful palliation by systemic to pulmonary artery anastomoses for hypoxia, a balloon atrial septostomy should probably be performed at the initial cardiac catheterization. Furthermore, since Fontan and Baudet[13] have achieved right ventricular bypass in the patient with tricuspid atresia, every effort should be made to allow these patients to reach the age when conduit surgery can be performed.

Intermittent obstruction of the mitral valve by the aneurysmal dilatation of the atrial septum is possible, and this diagnosis should be considered when findings consistent with intermittent mitral stenosis develop in a patient with tricuspid atresia. In this regard, the similarity of the findings to those of a pedunculated left atrial myxoma is obvious.

Finally, although we have described aneurysmal dilatation of the interatrial septum in a patient with tricuspid atresia, atrial restriction is similarly common in the patient with mitral atresia. In this situation, the valve of the foramen ovale may herniate into the right atrium and aneurysmal dilatation may occur.

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Diagnostic Considerations in Electromechanical Dissociation

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Cardiac electromechanical dissociation in the intact animal refers to a phenomenon in which adequate electrocardiographic complexes are recorded when effective cardiac output has ceased. Such findings in man are almost invariably associated with a fatal outcome although one can observe this phenomenon in potentially treatable disorders. Recognition of these disorders on the basis of certain clinical and electrocardiographic findings may be of clinical importance.

Three kinds of hemodynamic alterations can produce electromechanical dissociation: inadequate preload, excessive (obstructive) afterload and depressed cardiac muscle or "pump" performance. A precipitous decrease in preload leading to electromechanical dissociation can occur in exsanguinating hemorrhage, an inflow-obstructing atrial myxoma or acute cardiac tamponade; severe outflow obstruction producing electromechanical dissociation can occur in pulmonary or aortic stenosis and massive pulmonary embolism; and cardiac "pump" dysfunction with electromechanical dissociation can occur as a result of a diffuse myocardial process, extensive ventricular asynergy or disruption of the integrity of the heart itself, for example, in rupture of a papillary muscle or the interventricular septum.

The clinical and electrocardiographic features that distinguish the common causes of electromechanical dissociation are shown in Table I. When electromechanical dissociation is associated with tachycardia, pump failure is not the only explanation; hemorrhage and massive pulmonary embolism are alternative possibilities. These two disorders can be distinguished by recording a venous pressure. When an acute massive hemorrhage produces electromechanical dissociation, venous pressure will be decreased, whereas in massive pulmonary embolism it will generally be increased.

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Another clue during a cardiac arrest that might suggest an occult exsanguinating hemorrhage is the apparent response to vasopressors only when these agents are administered as a "wide-open" infusion. When the rate of fluid administration is reduced, blood pressure abruptly disappears. In this situation, it is probably the acute volume expansion rather than the vasopressor that is maintaining blood pressure. When the triad of electromechanical dissociation, tachycardia and abdominal distension is present, a ruptured abdominal aneurysm should be considered. In three cardiac arrests I observed, this triad was present and autopsy confirmed the diagnosis of ruptured abdominal aneurysm.

When electromechanical dissociation is associated with bradycardia, activation of a vagally mediated depressor reflex is a likely possibility.[1] In fact, the occurrence of sinus bradycardia with *hypotension* should suggest either a primary vagal effect or an inappropriate heart rate response to a decrease in blood pressure. Such blunted heart rate responses are observed in the "sick sinus syndrome," or after treatment with beta- or ganglionic blocking agents. The sudden occurrence of electromechanical dissociation and bradycardia, especially in a clinical setting that might be associated with acute cardiac compression—for example, after cardiac surgery, chest injury or myocardial infarction—should suggest acute cardiac tamponade.[2] Although the occurrence of electromechanical dissociation and bradycardia was originally described in the setting of cardiac rupture,[2] recent experimental studies[3] have demonstrated that the bradycardia of cardiac rupture is a characteristic finding in the late phase of acute cardiac tamponade in dogs. Vagotomy[3] or administration of atropine[1] reverses the bradycardia, and in the vagotomized dog acute cardiac tamponade does not produce bradycardia until anoxic slowing ensues.[3] These findings appear to be more than a physiologic curiosity associated with experimental cardiac tamponade. Administration of atropine at the time of the bradycardic effect increased left ventricular systolic pressure, improved various indexes of left ventricular performance and permitted a greater pericardial volume before the

TABLE I

Clinical and Electrocardiographic Findings of the Common Causes of Electromechanical Dissociation

Hemodynamic Alteration	Disorders	Heart Rate	Venous Pressure	Associated Electrocardiographic Findings
Reduced preload	Exsanguinating hemorrhage	Tachycardia	Low	
	Acute cardiac tamponade	Bradycardia	High	Low QRS voltage; prominent P waves; QRS axis shift; S-T and T changes; electrical alternans
Acute outflow obstruction	Pulmonary embolism	Tachycardia	High	Findings of right-sided overload
Pump failure	Acute myocardial infarction Cardiomyopathy	Tachycardia or Bradycardia	High	Frequently associated with atrioventricular block or intraventricular conduction abnormality, or both

occurrence of electromechanical dissociation.[1] Such changes were not produced by atrial pacing at a rate comparable with that produced by administration of atropine.[1]

These experiments also demonstrated other electrocardiographic features that might assist in the diagnosis of cardiac tamponade[4]: (1) QRS complex voltage recorded on surface leads decreased when intracardiac voltages increased; (2) P wave voltage did not change until the late phases of tamponade; (3) left axis deviation occurred in 6 of the 12 dogs studied and electrical alternans in 3; (4) striking T wave inversions and S-T junction elevations occurred, especially with rapid rates of infusion; and (5) S-T segment elevations developed when tamponade was prolonged. Except for alteration of the QRS axis and the dissimilar effect of cardiac tamponade on the QRS complex and P wave, these findings have previously been observed in clinical acute cardiac tamponade.[2] Thus, when these electrocardiographic findings are observed with electromechanical dissociation and bradycardia the diagnosis of acute cardiac tamponade is a possibility.

Clinical implications: It should be clear from this discussion that the finding of electromechanical dissociation during a cardiac arrest is not necessarily a hopeless clinical situation. Its occurrence with tachycardia might indicate an exsanguinating hemorrhage or a massive pulmonary embolism, whereas its occurrence with bradycardia might indicate cardiac tamponade, especially when accompanied by the electrocardiographic findings presented here. Thus, although electromechanical dissociation is frequently associated with extensive, irreversible cardiac injury and a grave prognosis, such findings can also be produced by conditions whose recognition and prompt treatment can result in a favorable outcome.

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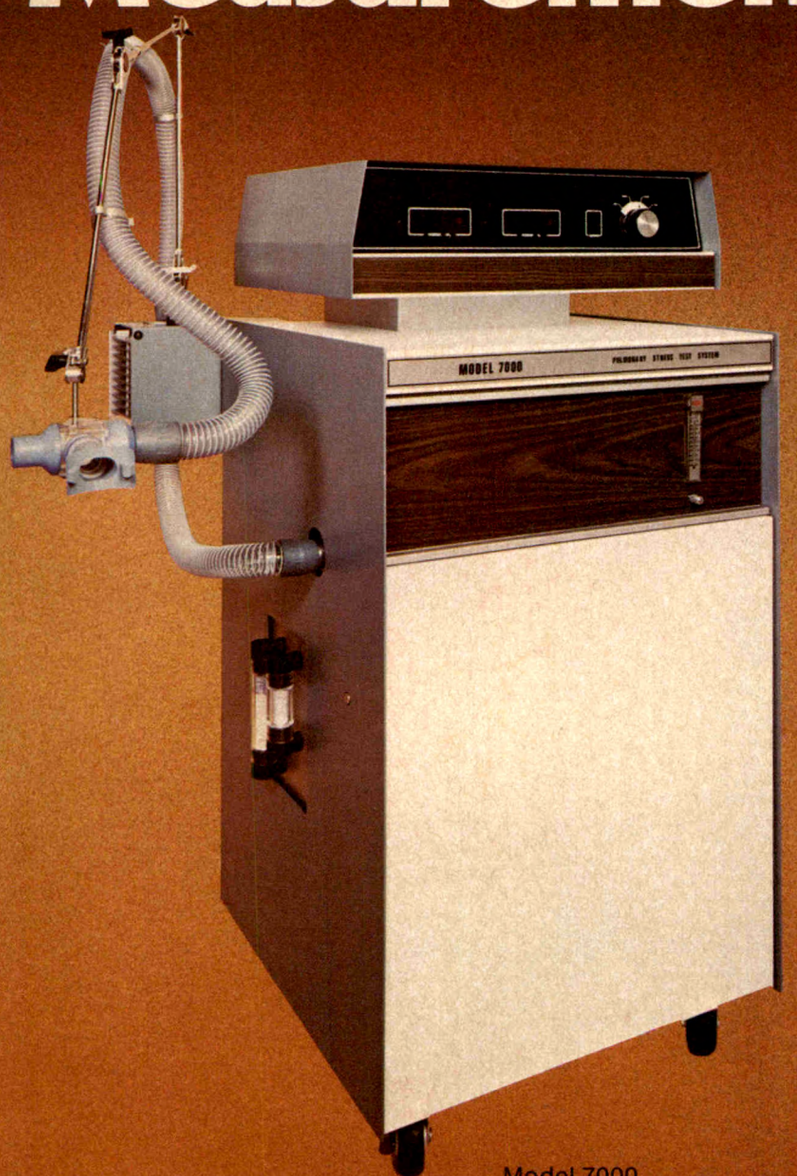

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Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

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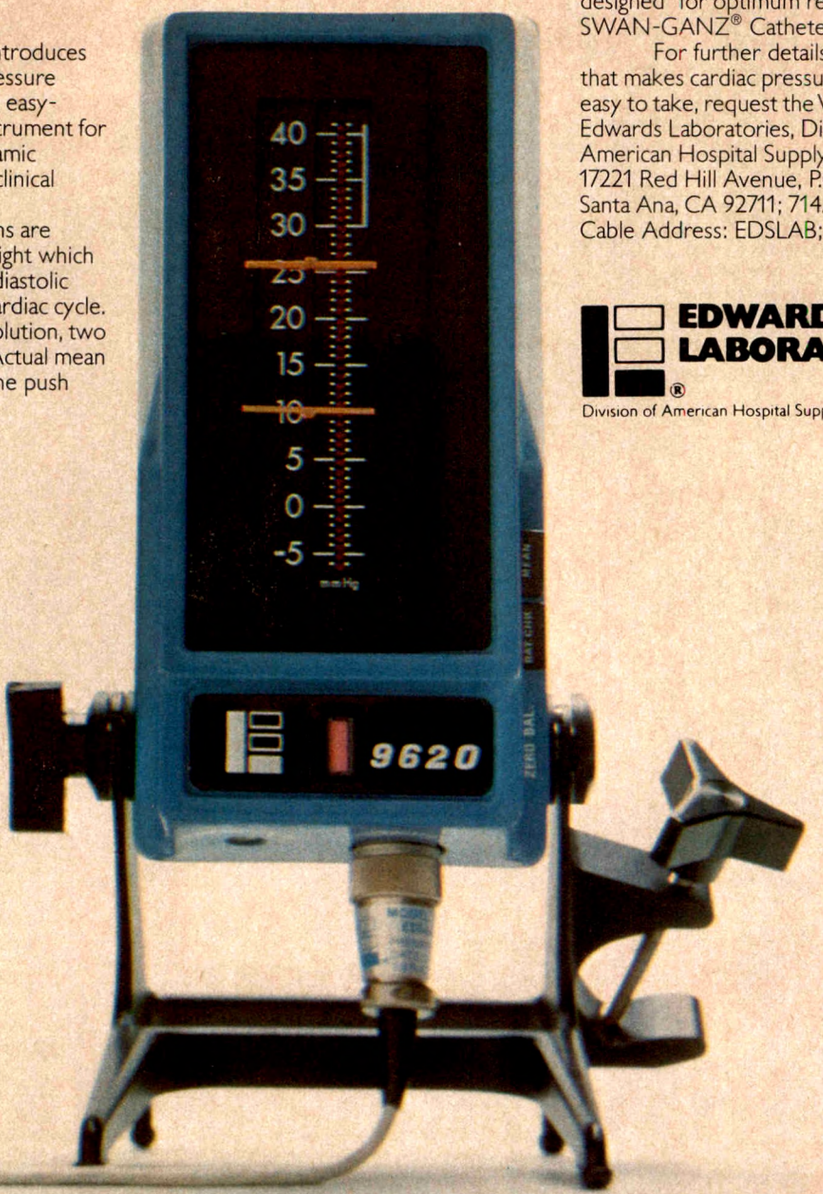

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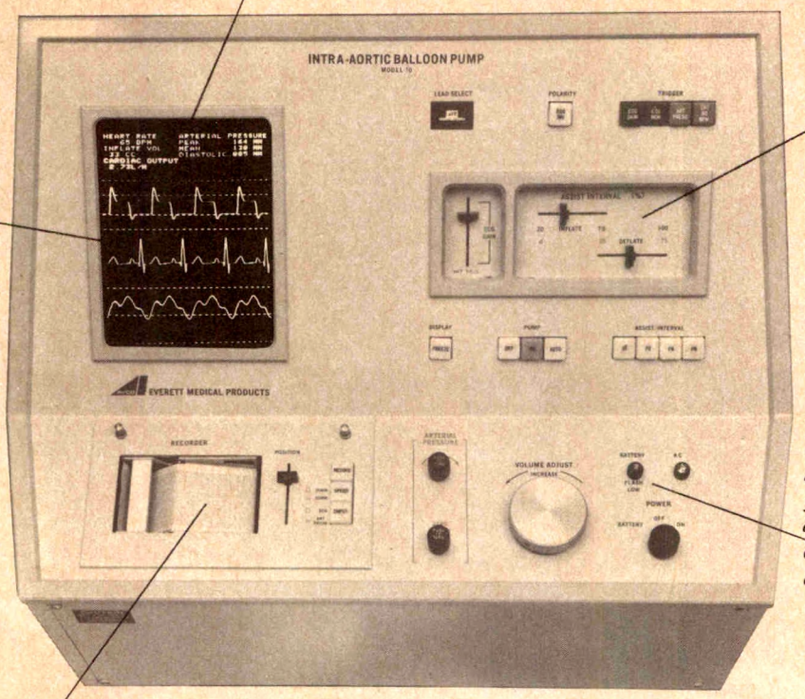

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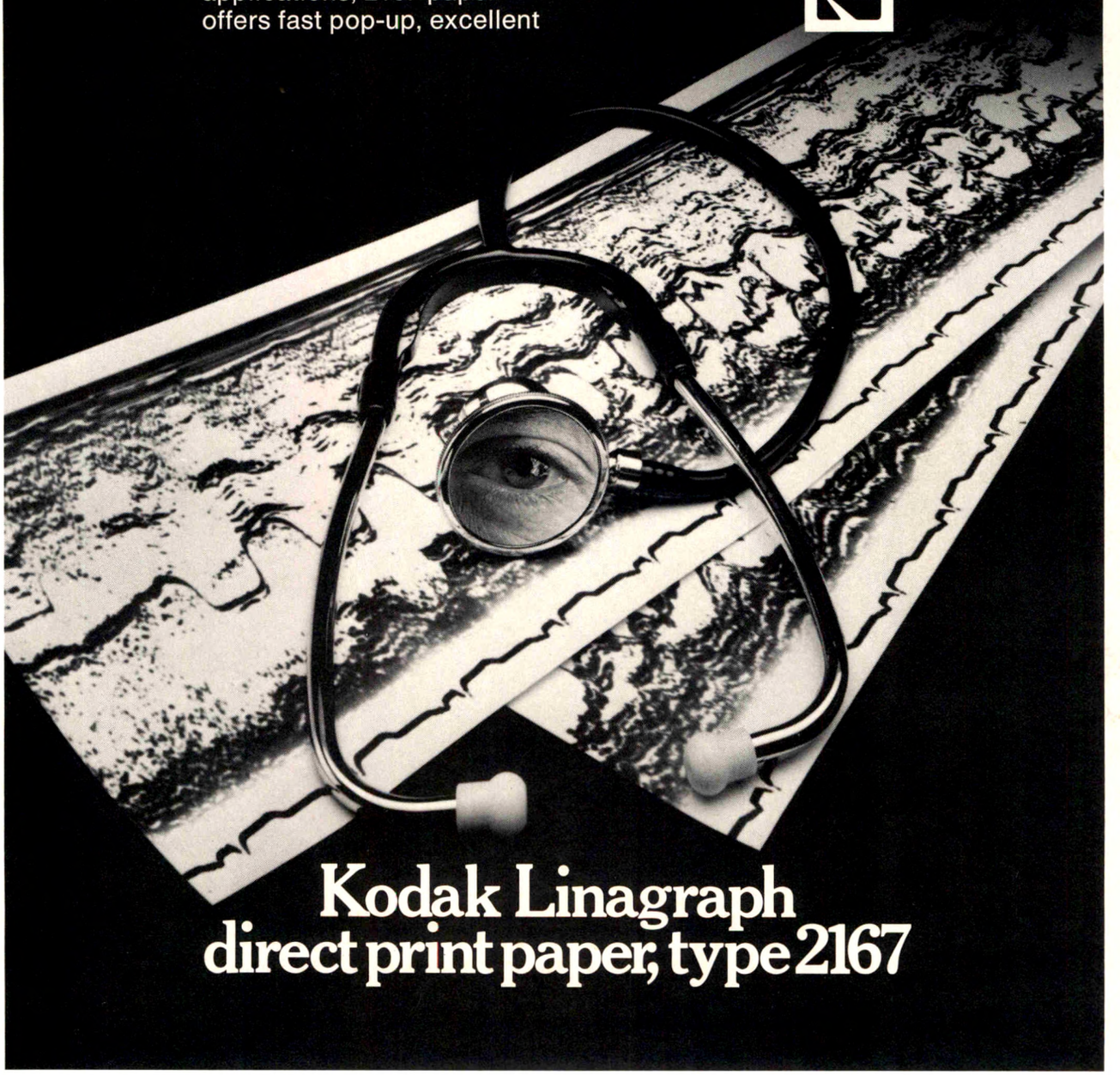

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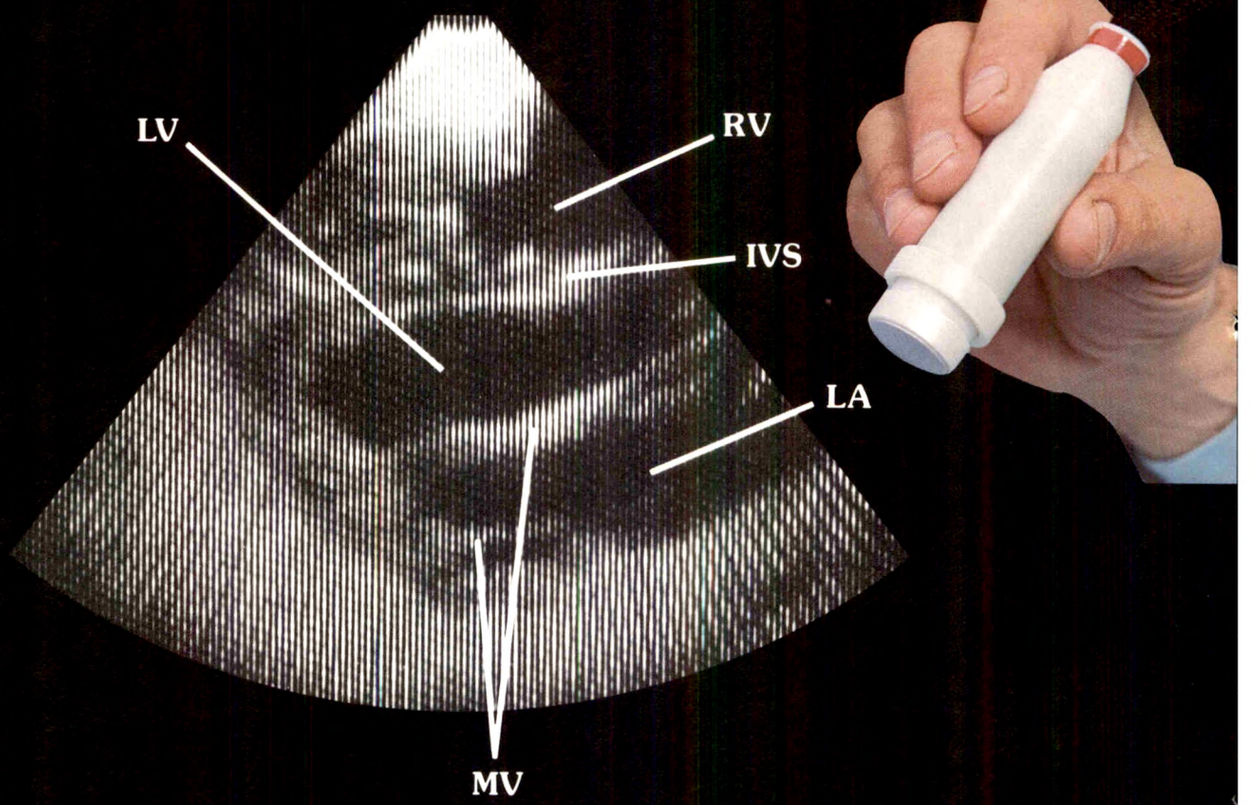

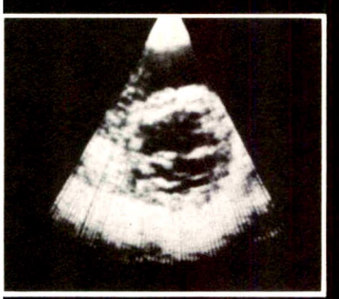

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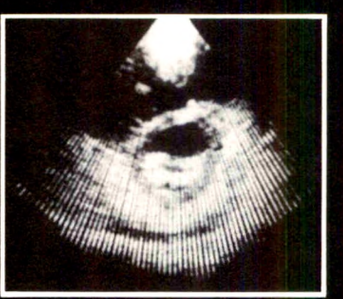
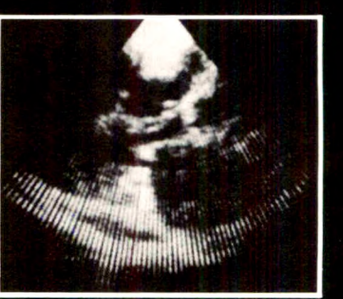


Transverse section of left ventricle with stenotic mitral valve.



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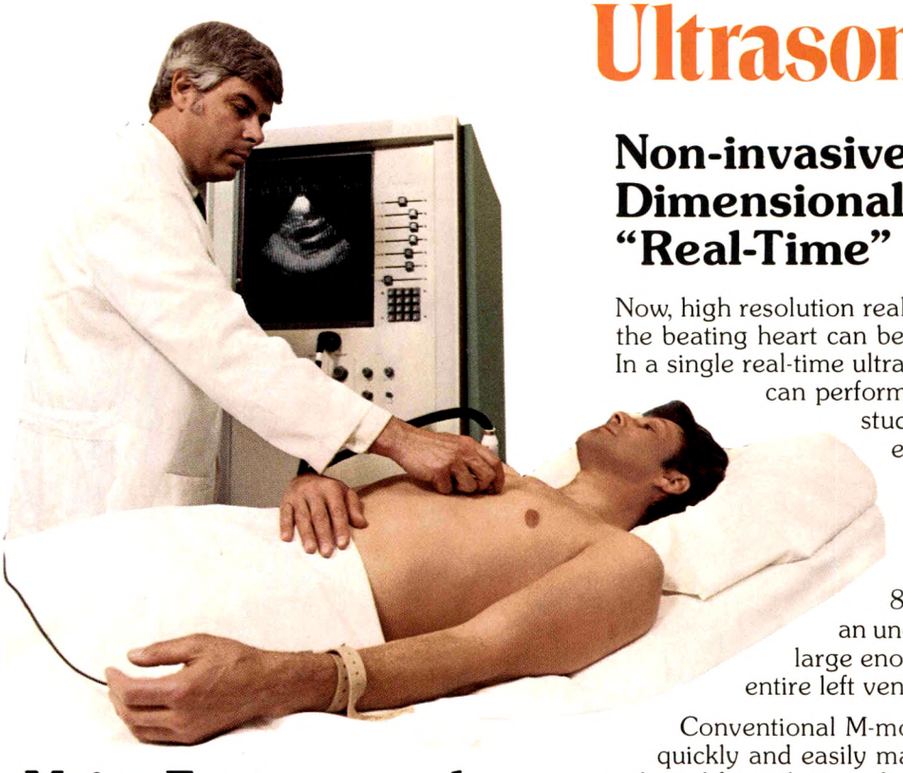

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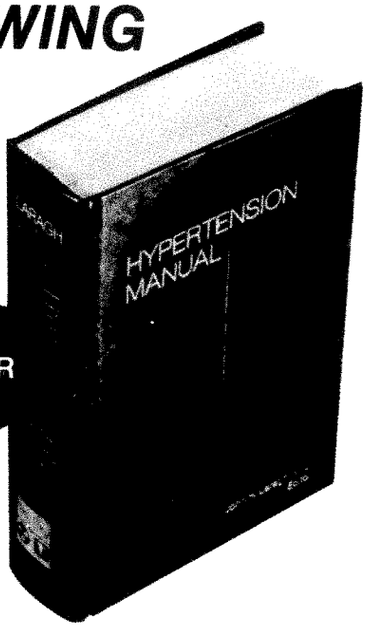

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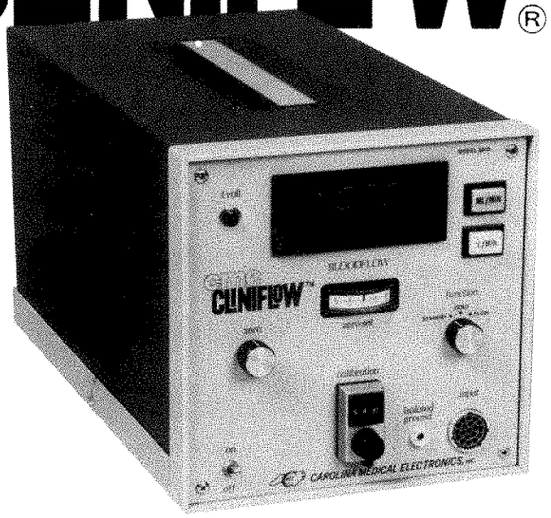

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LETTERS TO THE EDITOR

MITRAL VALVE PROLAPSE-CLICK SYNDROME—I

I believe the explanation offered by Jeresaty[1] for increased tension in the papillary muscles in the mitral valve prolapse syndrome is incorrect and adds to the general confusion surrounding Laplace's law. This law expresses the relation between tangential tension and intracavitary pressure. In the example under discussion the tangential forces are within the mitral valve itself and not the chordae tendineae or papillary muscles, which are oriented in a radial direction.

Increased tension may well be present in both chordae and papillary muscles in this syndrome. However, it can be explained by the increased surface area of the ballooning mitral leaflet. This can be expressed as follows: $A \times P = T(P)$ where A equals area of mitral valve in systole, P equals ventricular systolic pressure and T(P) equals total tension on papillary muscles. The tension in individual papillary muscles would depend upon the area of the mitral valve to which its chordae tendineae are attached. The actual tension within the mitral valve itself could actually be less than normal, this being entirely dependent upon its radius of curvature in systole.

Patrick J. McCormick, MD
Department of Cardiology
Little Company of Mary Hospital
Evergreen Park, Illinois

Reference

1. **Jeresaty RM:** Etiology of the mitral valve prolapse-click syndrome. Am J Cardiol 36: 110–113, 1975

REPLY

Pocock and Barlow[1] invoked Laplace's law to explain the increased tension transmitted to the papillary muscle by way of the chordae tendineae. I agree that this law applies to the mitral valve itself and not to the chordae tendineae or papillary muscles. Unlike McCormick, I believe that actual tension within the redundant and voluminous mitral cusps could be more than normal because of their large radius of curvature in systole. I am glad that McCormick provides another explanation for the increased tension in both chordae and papillary muscles in this syndrome, namely, "increased surface area of the ballooning mitral leaflet."

Robert M. Jeresaty, MD, FACC
St. Francis Hospital
Hartford, Connecticut

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1. **Pocock WA, Barlow JB:** Etiology and electrocardiographic features of the billowing mitral leaflet syndrome. Analysis of a further 130 patients with a late systolic murmur or nonejection systolic click. Am J Med 51:731–739, 1971

MITRAL VALVE PROLAPSE-CLICK SYNDROME—II

The mitral valve prolapse-click murmur syndrome is currently being discussed extensively in hallways and in journals. Despite this, I believe that the following points are not generally appreciated.

1. The mitral valve prolapse-click murmur syndrome is *common.* In years past rheumatic fever and rheumatic heart disease were common and the click murmur syndrome was not appreciated as a mitral valve problem. It followed that almost all mitral systolic murmurs were thought to be due to rheumatic heart disease. Today rheumatic fever and rheumatic heart disease are less common in the United States and we do recognize the click murmur syndrome. Therefore, it is proper to consider nonrheumatic causes of mitral regurgitation when one hears a systolic murmur (with or without a click) at the apex of the heart.

2. The cause of the mitral valve prolapse-click murmur syndrome is considered to be *myxomatous degeneration* of the mitral valve leaflets and chordae tendineae.[1] There may be other causes of this syndrome. I suspect, too, that systolic mitral clicks are not always accompanied by significant mitral valve prolapse.

3. Five points should be made about the recognition of the mitral valve prolapse-click murmur syndrome.

A. Now that it is recognized that the condition is a common syndrome and that one should not instantly declare a rheumatic origin when a systolic murmur is heard at the apex (with or without a click) it is likely that the condition will be recognized more frequently.

B. The majority of patients have no symptoms. Only a few patients with the full-blown syndrome have arrhythmias and chest pain that simulates angina pectoris.

C. To identify a systolic click, a click-systolic murmur or a systolic murmur emanating from the mitral valve it is necessary to listen with the stethoscope at the cardiac apex while the patient is standing up. For generations every physician was taught that he had not listened to the cardiac apex unless the apex had been listened to while the patient was in the left lateral recumbent position after exercise. The murmur of mitral stenosis is accentuated when these maneuvers are implemented. *It is clear now that we have not listened to systole at the apex unless the apex is listened to while the patient stands. This maneuver will often accentuate the systolic click and murmur and cause them to occur earlier in systole.* A questionable diagnosis may become definite as a result of this action.

D. Some patients with chest pain simulating angina pectoris and T wave abnormalities in the electrocardiogram have the mitral valve prolapse-click murmur syndrome. And some patients without chest pain have T wave abnormalities associated with the mitral valve prolapse-click murmur syndrome. One must not jump instantly to a diagnosis of coronary atherosclerosis in either case but should search for other disorders including the mitral valve prolapse-click murmur syndrome.

E. The echocardiogram is a remarkable tool. It is my current view that there may be echocardiographic evidence of mitral valve prolapse without corresponding physical findings and that there may be the physical signs of click murmur syndrome without definite echocardiographic evidence of prolapse of the mitral valve.

4. The view that patients with systolic clicks (with or without a murmur) have a very poor prognosis must be changed. The majority of patients with these findings have an excellent prognosis and do *not* have troublesome arrhythmias, chest pain, heart failure, chordal rupture or sudden death. The incidence rate of endocarditis is quite low, and the need for mitral valve surgery is rare. Patients with this syndrome are not all alike. Internists and cardiologists probably see the more severe cases. The serious complications mentioned earlier do occur and the few patients with progressive and intractable problems despite treatment with propranolol may require the surgical placement of a new mitral valve. The

point is that most patients don't have these complications and must not be frightened unnecessarily.

As pointed out by Cobbs, patients with myxomatous disease of the aortic valve producing severe progressive aortic regurgitation and with myxomatous disease of the mitral valve producing severe progressive mitral regurgitation belong in a more serious category of patients than patients with unchanging or slowly progressive mitral systolic click murmur syndrome.[1,2]

5. I have seen several patients who were frightened by the terms applied to this syndrome. One distressed lady said, "I have a floppy valve." Another said, "I have a click or pop and a prolapse." Intelligent patients are reading the medical journals and become quite disturbed because of the emphasis placed on sudden death and the troublesome complications that a few patients with severe prolapse have. A major purpose of this communique is to urge the use of the name Barlow's syndrome[3] in order to avoid the use of frightening terms and to urge everyone to view the syndrome without undue emphasis on the uncommon subset of patients who have serious difficulties associated with the condition. Perhaps the term Read's syndrome of the aortic valve and Read's syndrome of the mitral valve should be used to refer to the more serious progressive conditions.[1,2] Whereas I do not champion the use of eponyms, they are useful when one wishes to convey that a certain condition exists and that the alternative identifying terms are frightening or lengthy. Witness the use of the term Down's syndrome rather than mongolism.

The cardiology group in the Department of Medicine of Emory University School of Medicine has been interested in the mitral valve prolapse-click murmur syndrome for many years.[1,4,5,6] Woodfin Cobbs of our group wrote the chapter for the second edition of The Heart in 1969 and it was published in 1970.[4] He updated the material for the third edition in 1973 and it was published in 1974.[1] I ask the readers of this letter to carefully check pages 882, 887, 1116 of the third edition and to determine if we have "accepted the unproved concept of the causal linking between coronary artery disease and the click syndrome" as stated by Jeresaty in his editorial. We indicated that myxomatous degeneration of the valve was the cause of the condition (see page 882 of the third edition).[1] We did indicate on page 1116 in the third edition that the murmur of papillary muscle dysfunction may be preceded by a click.[1] We did not claim that there was a "causal linking between coronary artery disease and the click syndrome." We placed that single sentence in the text in deference to those who have heard such a click in patients with infarction.[7] Note carefully on page 891 in the third edition of The Heart that Cobbs writes:

> Midsystolic clicks may also occur in coronary artery disease, and even the complete click late-systolic murmur syndrome (described earlier in this section) has been ascribed to it.[6] Such a causal relation, however, would be difficult to establish except with careful serial observations begun before the myocardial infarction. Spontaneous variation of the physical findings in the idiopathic cases might account for a sudden "appearance" at any particular time. Since the idiopathic (Barlow's) syndrome is rather common, one would expect that it might coexist frequently with coronary artery disease and that the two could interact in interesting ways. Very likely the association of Barlow's syndrome with coronary artery disease is a mixture of causality and chance. If, however, one should regard this syndrome as possible evidence for ischemic heart disease,[6] diagnostic confusion might result, since significant numbers of such patients have chest pain variably suggestive of angina pectoris in the absence of coronary atherosclerosis.

For many years (since 1967) Cobbs has written about the mitral valve prolapse-click murmur syndrome. He first suggested that increased papillo-chordal stress was the main cause of its sporadic but distinctive clinical manifestations.[4] I urge readers to survey his work.[1,4,6]

J. Willis Hurst, MD, FACC
Department of Medicine
Emory University School of Medicine
Atlanta, Georgia

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1. **Cobbs BW Jr:** Clinical recognition and medical management of rheumatic heart disease and other acquired valvular disease. In, The Heart, 3rd edition (Hurst JW, ed). New York, McGraw-Hill, 1974, p 880–889, 1116
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7. **Steelman RB, White RS, Hill JC, et al:** Midsystolic clicks in arteriosclerotic heart disease: a new facet in the clinical syndrome of papillary muscle dysfunction. Circulation 44: 503–515, 1971

REPLY

I agree with most of Hurst's observations as to the prevalence, clinical features and differential diagnosis of the mitral valve prolapse-click syndrome.[1] He has rightfully stressed the benign outlook in these patients. In another paper, I have reached the same conclusion: "A review of my series would confirm the assessment of Allen et al. of the benign nature of this syndrome. The risk of sudden death is remote in this syndrome and therefore should not be mentioned to the patient or his family for fear of inducing undue anxiety and neurosis."[2]

While recognizing the major contributions of Barlow and Read, I do not believe that their names should be used to designate the benign and "the more serious progressive condition," respectively. I do not believe that "Barlow's syndrome" is more reassuring to a frightened patient than "click syndrome" or "mitral valve prolapse." In this syndrome, eponyms should not be championed because, until proved otherwise, the benign and the severe forms probably are part of a spectrum and do not represent separate disease entities. The patient with a benign form may become symptomatic as a result of progression of mitral insufficiency, rupture of chordae tendineae, bacterial endocarditis, and other factors. There is no good correlation between symptoms, auscultatory, electrocardiographic, echocardiographic and angiographic findings. I am sure that Hurst would not advocate using eponyms to separate benign from malignant forms of hypertension and asymptomatic coronary artery disease from the form associated with angina, myocardial infarction or heart failure.

Excellent work on mitral valve prolapse has been carried out by the cardiology group at Emory University School of Medicine, particularly by Woodfin Cobbs. Hurst points out that Cobbs "first suggested that increased papillo-chordal stress was the main cause of its sporadic but distinctive clinical manifestations." Pocock and Barlow, and I[3] in an article submitted for publication in 1970, have independently proposed the same theory.

The main point of disagreement between Hurst and me is

the emphasis placed on the relation between coronary artery disease and the click syndrome in the third (1974) edition of his excellent book. The following quotations will prove my point:

Page 269: "Systolic clicks may introduce the late systolic murmur of papillary muscle dysfunction in ischemic heart disease."

Page 887: "Lower-pitched midsystolic sounds sometimes introducing murmurs may occur in coronary artery disease. Sharp clicks have also been reported."

Page 1024 (under the heading Mitral Regurgitation associated with Myocardial infarction): "Papillary muscle dysfunction or dysfunction of the ventricular myocardium adjacent to the origin of third-order chordae tendineae may also occasionally *result* in the characteristic syndrome with a midsystolic click and a mid- or late systolic murmur associated with mitral regurgitation."

Page 1116 (in the chapter on Coronary Artery Disease and under the heading Papillary muscle dysfunction): "The systolic mitral murmur may be delayed after the first sound, may be initiated with a systolic click and may have a crescendo configuration."

Page 891 (quoted by Hurst in his letter): "Very likely the association of Barlow's syndrome with coronary artery disease is a mixture of *causality* and chance."

I respectfully maintain that these quotations can be construed as an acceptance of the "unproved concept of the causal linking between coronary artery disease and the click syndrome." They do not represent merely "a single sentence in the text in deference to those who have heard such a click in patients with infarction." In my editorial and other publications[1,4,5] I had concluded that there was a "coincidental rather than causal association" between coronary artery disease and mitral valve prolapse. I am happy to learn that Hurst, in his letter, agrees with this conclusion.

Robert M. Jeresaty, MD, FACC

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Current Techniques in Extracorporeal Circulation, edited by M. I. Ionescu, MD, FACS and G. H. Wooler, TD, MD, MA, FRCS. London, Butterworth, 1976, 570 pages, $36.14

D'Abreu's Practice of Cardiothoracic Surgery, fourth edition, by J. Leigh Collis, MD, BSc, FRCS, D. B. Clarke, MB, ChB, FRCS and R. Abbey Smith, ChM, FRCS. Baltimore, Williams & Wilkins, 1976, 710 pages, $77.00

Fundamentals of Vascular Radiology, by Robert I. White, Jr., MD. Philadelphia, Lea & Febiger, 1976, 151 pages, $13.00

Gibbon's Surgery of the Chest, third edition, by David C. Sabiston, Jr., MD and Frank C. Spencer, MD. Philadelphia, W. B. Saunders, 1976, 1592 pages, $67.50

Handbook of Experimental Pharmacology. Volume 16, Experimental Production of Diseases, Part 3, Heart and Circulation, edited by J. Schmier and O. Eichler. New York, Springer-Verlag, 1975, 600 pages, $125.00

The Lung in the Critically Ill Patient. Pathophysiology and Therapy of Acute Respiratory Failure, edited by William C. Shoemaker, MD. Baltimore, Williams & Wilkins, 1976, 129 pages, $9.50

Mechanisms of Contraction of the Normal and Failing Heart, second edition, by Eugene Braunwald, MD, MA, John Ross Jr., MD and Edmund H. Sonnenblick, MD. Boston, Little Brown, 1976, 417 pages, $24.50

Monographs on Atherosclerosis. Bile Acids. Chemistry and Physiology of Bile Acids and Their Influence on Atherosclerosis, volume 6, by William T. Beher, series edited by David Kritchevsky, O. J. Pollak and Henry S. Simms. Basel, S. Karger, 1976, 225 pages, $39.00

Myocardial Revascularization. A Surgical Atlas, by Quentin R. Stiles, MD, Bernard L. Tucker, MD, George G. Lindesmith, MD and Bert W. Meyer, MD. Boston, Little Brown, 1976, 165 pages, $32.50

Noninvasive Evaluation of Human Circulation, by J. Simonyi, MD, CSc, with the contribution of J. Fischer. Budapest, Akademiai Kiado, 1976, 251 pages, $15.00

The Principles and Practice of Medicine, 19th edition, edited by A. McGehee Harvey, MD, DSc, Richard J. Johns, MD, Albert H. Owens, Jr., MD and Richard S. Ross, MD. New York, Appleton-Century-Crofts, 1976, 1892 pages, $33.50

Stedman's Medical Dictionary, illustrated, 23rd edition. Baltimore, Williams & Wilkins, 1976, 1678 pages, $21.95

Techniques in Bedside Hemodynamic Monitoring, by John Speer Schroeder, MD and Elaine Kiess Daily, RN, RCVT. Saint Louis, C. V. Mosby, 1976, 212 pages, $7.25

Understanding Electrocardiography. Physiological and Interpretive Concepts, second edition, by Mary H. Conover, RN, BSMEd and Edwin G. Zalis, MD, FACP, FACC, FCCP. Saint Louis, C. V. Mosby, 1976, 241 pages, $7.50

Vascular Surgery. Principles and Techniques, by Henry Haimovici, MD. New York, McGraw-Hill, 1976, 967 pages, $55.00

Norms for Use in Peer Review of Selected In-Hospital Cardiovascular Diagnoses

Revised by the American College of Cardiology
Bethesda, Maryland
February 1976 *

FOREWORD

Norms prepared by the American College of Cardiology for use in peer review of the quality of cardiovascular practice have been previously published (*American Journal of Cardiology* 33:697–709, 1974; 36:125–127, 1975), and the latter Norms were those included in the preliminary document *Model Screening Criteria to Assist PSRO's*, May, 1975.

This document has been revised, and the Norms which follow represent the criteria sets revised by the American College of Cardiology. A new format has been employed, another cardiovascular diagnosis added, and overlaps with criteria sets developed by other specialty societies have been resolved.

Items I and II serve for Concurrent Review; Items V and VI for Retrospective Review; Items III and IV, though intended primarily for Retrospective Review, may also serve for Concurrent Review.

The Norms will be included in the revised edition of *Model Screening Criteria to Assist PSRO's*.

Regional PSRO's may accept these criteria for peer review, or they may modify them or generate their own local criteria. The official position of the American College of Cardiology toward PSRO is explained in the original publication.

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* *Members of the American College of Cardiology Cardiovascular Norms Committee are: R. Joe Noble, MD, FACC, Chairman; Maxwell G. Berry, MD, FACC; Louis Gillespie, Jr., MD, FACC; Brendan Phibbs, MD, FACC; Arthur Selzer, MD, FACC; and Sylvan L. Weinberg, MD, FACC.*

Address for reprints: Mr. William D. Nelligan, Executive Director, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

DIAGNOSIS/PROBLEM:
HEART FAILURE, CONGESTIVE
Code Numbers: *H-ICDA*, 427.1, 427.9
***ICDA-8* 427.0, 427.1, 782.4**

I. *Admission Review*
  A. Reasons for admission
    1. Diagnosis or suspicion of pulmonary edema
    2. Newly diagnosed congestive heart failure, to establish response to therapy
    3. Unresponsive to outpatient management (i.e., persistent or recurrent symptoms of dyspnea, weakness, edema)
    4. Diagnostic admission (i.e., to establish etiology, functional significance of lesion, anatomic or physiologic derangement) (e.g., scheduled for cardiac catheterization)

II. *Continued Stay Review*
  A. Reasons for extending the initial length of stay
    1. Persistent symptomatology (i.e., refractory heart failure)
    2. Pulmonary embolization (See criteria set for pulmonary embolization)
    3. Renal insufficiency and/or electrolyte imbalance
    4. Arrhythmia (See criteria set for atrial fibrillation)
    5. Myocardial infarction (See criteria set for myocardial infarction)

III. *Validations of:*
  A. Diagnosis
    1. Radiologic evidence of congestive heart failure
    2. Positive physical findings of gallop rhythm, or venous hypertension, edema or enlarged heart
    3. Clinical improvement following digitalis or diuretics
  B. Reasons for admission
    1. Validation of diagnosis (See IIIA 1, 2, 3) and historical documentation that the condition is newly recognized (IA-2) or unresponsive to outpatient management (IA-3)
    2. Serious clinical disability (dyspnea, edema, weakness, murmur) (IA-4)

IV. *Critical Diagnostic and Therapeutic Services*
  A. Electrocardiogram (100%)
  B. Radiologic examination of the chest (100%)
  C. Serum electrolyte, and blood urea nitrogen or creatinine (100%)

V. *Discharge Status*
  A. Improvement in symptoms (III B-2); and signs (III A-2)
  B. Documented plan of follow-up

VI. *Complications*
  A. Primary disease and treatment—specific complications
    1. Rising blood urea nitrogen or creatinine
    2. New arrhythmia, interpreted as consistent with digitalis intoxication
    3. Digitalis toxicity (digoxin level over 4 ng/ml; digitoxin level over 40 ng/ml)
  B. Nonspecific indicators
    1. Surgery

DIAGNOSIS/PROBLEM:
ATRIAL FIBRILLATION
(Criteria Applicable to Other Arrhythmias)
Code Numbers: *H-ICDA* 415.1, 415.2, 415.3, 415.4, 415.8, 415.9, 416.1, 416.2, 416.3, 416.4, 416.5, 416.6, 416.8
***ICDA-8* 427.2, 427.3, 427.4, 427.5, 427.6, 427.9**

I. *Admission Review*
  A. Reasons for admission
    1. Newly diagnosed
    2. Rapid rate requiring prompt slowing (or slow rate, with other arrhythmias)
    3. Failure to respond to ambulatory antiarrhythmic therapy
    4. Symptoms of chest pain, syncope, dyspnea or embolization
    5. Diagnosis or suspicion of ventricular arrhythmias

II. *Continued Stay Review*
  A. Reasons for extending the initial length of stay
    1. Chest pain (angina → infarction)
    2. Congestive failure or shock
    3. Unresponsive to initial therapy
    4. Serious ventricular arrhythmias

III. *Validations of:*
  A. Diagnosis
    1. Electrocardiographic documentation of rhythm disturbance
  B. Reasons for admission
    1. Historical, physical and electrocardiographic documentation of IA 1, 2, 3, 4 or 5

IV. *Critical Diagnostic and Therapeutic Services*
  A. Electrocardiogram (100%)
  B. Radiologic examination of the chest (100%)

V. *Discharge Status*
  A. Heart rate controlled within normal range
  B. Free of chest pain, syncope, dyspnea
  C. Documented plan of follow-up

VI. *Complications*
  A. Primary disease and treatment—specific complications
    1. New rhythm disturbance interpreted as consistent with drug intoxication
  B. Nonspecific indicators
    1. No entry appropriate

DIAGNOSIS/PROBLEM:
MYOCARDIAL INFARCTION, ACUTE
Code Numbers: *H-ICDA* 410
***ICDA-8* 410**

I. *Admission Review*
  A. Reasons for admission
    1. Diagnosis or suspicion of acute myocardial infarction

II. *Continued Stay Review*
  A. Reasons for extending the initial length of stay
    1. Persistent arrhythmia

2. Congestive heart failure or shock (See criteria set for heart failure, congestive)
3. Aneurysm, mitral regurgitation, ventricular septal perforation
4. Persistent or recurrent pain (including pericarditis)
5. Pulmonary embolization (See criteria set for pulmonary embolization)

III. *Validations of:*
A. Diagnosis
1. Electrocardiographic evidence of acute myocardial infarction
2. Elevation in serum cardiac enzymes (creatine phosphokinase [CPK], glutamic oxaloacetic transaminase [SGOT], lactic dehydrogenase [LDH], etc.)
3. Classic history and hospital course (e.g., chest pain, interpreted as consistent with myocardial infarction. No specific modifiers required)
B. Reasons for admission
1. No entry necessary

IV. *Critical Diagnostic and Therapeutic Services*
A. Monitoring of cardiac rhythm (100%)
B. Intravenous infusion line maintained (100%)
C. Coronary care unit, if available (100%)
D. Serial electrocardiograms and serial serum cardiac enzymes (100%)
E. Radiologic examination of the chest (100%)

V. *Discharge Status*
A. Alive
B. Pain-free
C. Documented plan of follow-up

VI. *Complications*
A. Primary disease and treatment—specific complications
1. Arrhythmia interpreted as consistent with digitalis intoxication
B. Nonspecific indicators
1. No entry appropriate

DIAGNOSIS/PROBLEM:
HEART DISEASE, ARTERIOSCLEROTIC (INCLUDE ANGINA PECTORIS, CHEST PAIN, AND CORONARY ARTERY DISEASE)
Code numbers: *H-ICDA* 412, 413
***ICDA-8* 412, 413**

I. *Admission Review*
A. Reasons for admission
1. Diagnosis or suspicion of unstable angina pectoris, including new angina pectoris
2. Scheduled for coronary angiography
3. Angina pectoris refractory to medical management
4. Scheduled for operation

II. *Continued Stay Review*
A. Reasons for extending the initial length of stay
1. Persistent, recurrent angina pectoris
2. Cardiac arrhythmias (See criteria set for atrial fibrillation)
3. Complications of diagnostic procedures (e.g., arterial occlusion, bleeding)
4. Myocardial infarction (See criteria set for myocardial infarction)
5. Postoperative complications (e.g., bleeding, infections, persistent cardiac failure, central nervous system complications)

III. *Validations of:*
A. Diagnosis
1. History of angina pectoris is sufficient
2. Electrocardiographic confirmation of myocardial infarction
3. Stress electrocardiographic test positive or resting electrocardiogram during spontaneous angina positive
4. Coronary angiographic confirmation
B. Reasons for admission
1. Suspicion of angina or positive electrocardiographic findings of ischemia (rest or exercise) (IA 1, 2)
2. Historical documentation of IA 3
3. Appropriate symptomatology with coronary angiographic confirmation of occlusive coronary artery disease (IA 4)
4. Appropriate symptomatology with coronary angiographic confirmation of ventricular aneurysm or mitral regurgitation (IA 4)

IV. *Critical Diagnostic and Therapeutic Services*
A. Electrocardiogram (100%)
B. Radiologic examination of the chest (100%)
C. Coronary angiography (for patients treated surgically) (100%)

V. *Discharge Status*
A. Alive
B. Condition clinically stable or improving
C. Documented plan of follow-up
D. Postoperative wound healing satisfactorily
E. Ambulatory

VI. *Complications*
A. Primary disease and treatment—specific complications
1. Complications of coronary angiography and catheterization (e.g., arterial occlusion, bleeding)
2. Postoperative complications (e.g., bleeding, wound infection, pulmonary complications, myocardial infarction, persistent cardiac failure)
B. Nonspecific indicators
1. Any extension of initial length of stay assignment
2. Second operation
3. Persistent fever

DIAGNOSIS/PROBLEM:
HEART DISEASE, VALVULAR
Code numbers: *H-ICDA* 424
***ICDA-8* 424**

I. *Admission Review*
A. Reasons for admission
1. Scheduled for cardiac catheterization

2. Valvular heart disease complicated by heart failure, chest pain, syncope, hemoptysis or emboli
3. Diagnosis or suspicion of aortic stenosis
4. Scheduled for operation

II. *Continued Stay Review*
A. Reasons for extending the initial length of stay
1. Arrhythmias or congestive heart failure (See appropriate criteria sets)
2. Bacterial endocarditis
3. Thromboembolism
4. Hemodynamically significant valvular lesion warranting surgery
5. Postoperative complications (e.g., wound infection, pneumonia, postpericardiotomy syndrome, atelectasis, pleural effusion)

III. *Validations of:*
A. Diagnosis
Documentation of any of the following:
1. Compatible radiologic evidence
2. Compatible phonocardiographic or echocardiographic evidence
3. Characteristic physical findings
4. Cardiac catheterization and angiocardiographic evidence
B. Reasons for admission
1. Presence of complicated valvular heart disease (e.g., congestive heart failure, chest pain, syncope or lightheadedness, hemoptysis or emboli) (IA 1, 2)
2. Congestive heart failure, dyspnea, chest pain, syncope, hemoptysis or embolization unresponsive to medical therapy (IA 1, 2, 4)
3. Validation of diagnosis of aortic stenosis (IA 3)

IV. *Critical Diagnostic and Therapeutic Services*
A. Electrocardiogram (100%)
B. Radiologic examination of the chest (100%)

V. *Discharge Status*
A. Alive
B. Anatomic diagnosis established
C. Ambulatory
D. Postoperative wound healing satisfactorily
E. Documented plan of follow-up

VI. *Complications*
A. Primary disease and treatment—specific complications
1. Complications of catheterization (e.g., arterial occlusion, bleeding)
2. Bacterial endocarditis developing during hospitalization
3. Postoperative complications (e.g., bleeding, infections, persistent cardiac failure)
B. Nonspecific indicators
1. Any extension of initial length of stay assignment
2. Tracheostomy
3. Second operation other than diagnostic procedure
4. Repeated blood administration after first postoperative day
5. Use of respirator for longer than 48 hours

DIAGNOSIS/PROBLEM
PERICARDIAL DISEASE
Code numbers: *H-ICDA* 420.0, 420.1, 420.2, 423.0 (use adhesive pericarditis only, not remainder of list), 423.1 (use constrictive only, not remainder of list), 423.9
***ICDA-8* 420, 423, 393**

I. *Admission Review*
A. Reasons for admission
1. Diagnosis or suspicion of acute pericarditis
2. Diagnosis or suspicion of pericardial tamponade
3. Scheduled for invasive diagnostic procedure
4. Scheduled for pericardiocentesis
5. Scheduled for operation

II. *Continued Stay Review*
A. Reasons for extending the initial length of stay
1. Persistent pain
2. Pericardial tamponade
3. Persistent pericardial effusion
4. Identification of specific etiologic agent or disease requiring inpatient diagnosis or therapy (e.g., tuberculosis, tumor)
5. Constrictive pericarditis

III. *Validations of:*
A. Diagnosis
1. Pericardial friction rub
2. Echocardiographic confirmation of pericardial effusion
3. Radiologic or nuclear imaging confirmation of pericardial effusion
4. Confirmation of pericarditis or pericardial effusion by pericardiocentesis or surgery
5. Compatible electrocardiographic evidence
B. Reasons for admission
1. Cardiac tamponade (IA 2, 3, 4, 5)
2. Constrictive pericarditis (IA 3, 4, 5)
3. Presence of pericardial fluid (IA 3, 4, 5)

IV. *Critical Diagnostic and Therapeutic Services*
A. Electrocardiogram (100%)
B. Radiologic examination of the chest (100%)
C. Echocardiogram (if available, 100%)

V. *Discharge Status*
A. Alive
B. No hemodynamic impairment (absence of venous hypertension, systemic hypotension)
C. Postoperative wound healing satisfactorily
D. Documented plan of follow-up

VI. Complications
A. Primary disease and treatment—specific complications
1. Complications of pericardiocentesis (bleeding, hemorrhage, tamponade, (pneumothorax)
2. Postoperative complications (e.g., bleeding, infection, persistent cardiac failure)
B. Nonspecific indicators
1. Persistent fever

DIAGNOSIS/PROBLEM
HYPERTENSION (INCLUDE ACCELERATED, ENCEPHALOPATHY)
Code numbers: *H-ICDA* 400, 438.3
***ICDA-8* 400, 436**

I. *Admission Review*
  A. Reasons for admission
    1. Diastolic blood pressure in excess of 110 mm Hg
    2. Failure to respond to antihypertensive therapy
    3. Neurologic or sensorium abnormalities
    4. Investigate secondary cause of hypertension (e.g., renal disease, renal vascular abnormality, adrenal disease)
    5. Uncontrolled congestive heart failure (see heart failure, congestive; renal failure [rising blood urea nitrogen])
  B. Initial length of stay assignment

II. *Continued Stay Review*
  A. Reasons for extending the initial length of stay
    1. Secondary cause of hypertension discovered (e.g., renal disease, renal vascular abnormality, adrenal disease)
    2. Unresponsive to initial antihypertensive therapy
    3. Neurologic abnormalities
    4. Congestive heart failure (See criteria set for heart failure, congestive)
    5. Renal failure (rising blood urea nitrogen or creatinine)
  B. Extended length of stay assignment

III. *Validations of:*
  A. Diagnosis
    1. Diastolic blood pressure in excess of 90 mm Hg
  B. Reasons for admission
    1. Historical documentation of IA 2
    2. Documentation of neurologic or sensorium abnormalities (IA 3)
    3. Documentation of renal, renal vascular or adrenal abnormality (IA 4)
    4. See criteria set for heart failure, congestive (IA 5)

IV. *Critical Diagnostic and Therapeutic Services*
  A. Blood pressure recorded daily, as a minimum (100%)
  B. Blood urea nitrogen or creatinine (100%)
  C. Electrocardiogram (100%)
  D. Fundoscopy (100%)
  E. Radiologic examination of the chest and intravenous pyelogram

V. *Discharge Status*
  A. Antihypertensive therapy (e.g., salt restriction, antihypertensive medication)
  B. Documented plan of follow-up
  C. Resolution of reason for admission

VI. *Complications*
  A. Primary disease and treatment—specific complications
    1. No entry appropriate
  B. Nonspecific indicators
    1. Surgery

Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

To be arranged individually **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

AUG. 28–30 **Tutorials in the Tetons (Second Annual)—Cardiac Emergencies.** Robert S. Eliot, FACC, director, and Robert J. Davis, FACC, Alan D. Forker, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Grand Teton National Park, Moran, Wyo.

SEPT. 8–10 **Venous Thrombosis Pulmonary Embolus Complex.** Orville Horwitz, FACC and Frank D. Gray, directors and Henry Berkowitz, H. James Day and L. Henry Edmunds, FACC, co-directors. The Hilton Hotel of Philadelphia, Philadelphia, Pa.

SEPT. 13–14 **Exercise Testing in Children and Young Adults.** Frederick W. James and Samuel Kaplan, FACC, directors. Children's Hospital Medical Center, Cincinnati

SEPT. 13–17 **Cardiology for the Consultant.** E. Grey Dimond, FACC, James E. Crockett, FACC and Don R. Santschi, FACC, directors. University of Missouri-Kansas City School of Medicine, Kansas City, Mo.

SEPT. 23–25 **The Clinical Spectrum of Adult Heart Disease.** Jonathan Abrams, FACC, director and Paul T. Cochran, FACC, co-director. Basic Medical Sciences Building of University of New Mexico Health Sciences Center, Albuquerque, N. Mex.

SEPT. 28–30 **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director. Indianapolis Hilton Hotel, Indianapolis, Ind.

OCT. 11–13 **Electrocardiography: Core Curriculum and Self-Assessment.** Leonard S. Dreifus, FACC, director. University City Holiday Inn, Philadelphia, Pa.

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OCT. 11–13 **Electrocardiography: Core Curriculum and Self-Assessment.** Alberto Benchimol, FACC, director. Safari Resort Hotel, Scottsdale, Ariz.

OCT. 12–14 **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Golden Gateway Holiday Inn, San Francisco, Calif.

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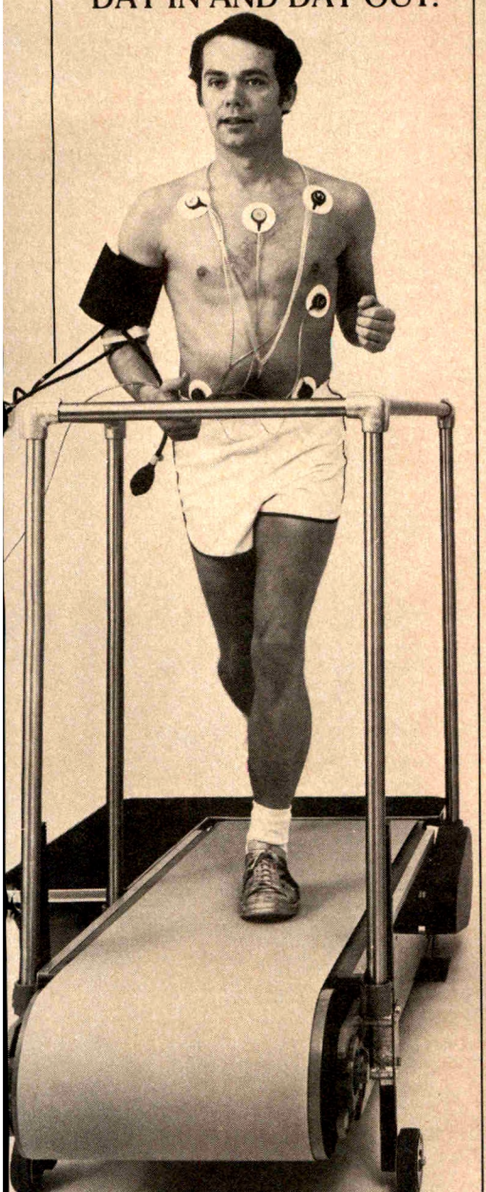

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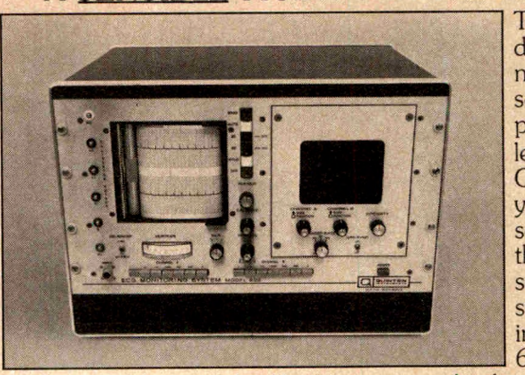

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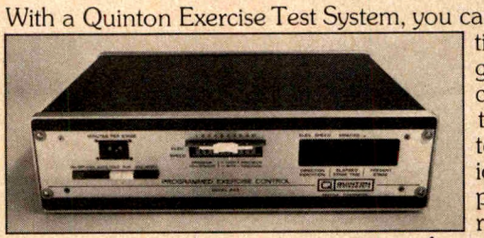

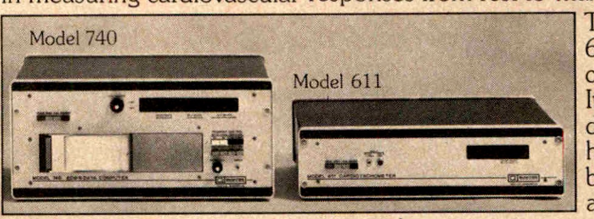

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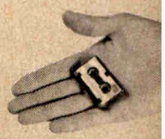

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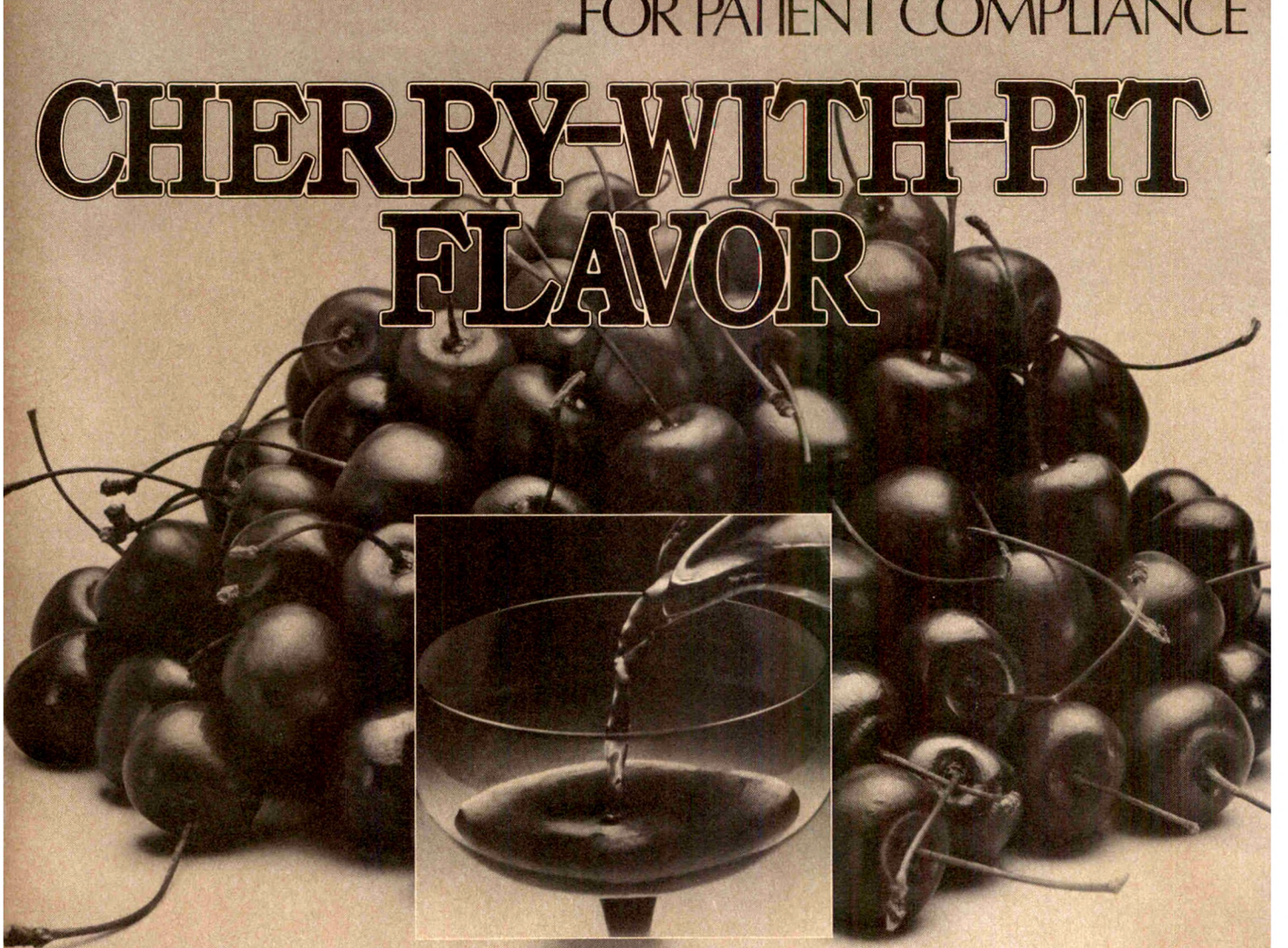

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(potassium chloride)

Klorvess® Combined Brief Summary

Klorvess (potassium chloride) 10% Liquid

Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol, 1%.

Klorvess Effervescent Tablets

Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove-plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration:

Klorvess® Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess® (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in 16-ounce and gallon bottles.

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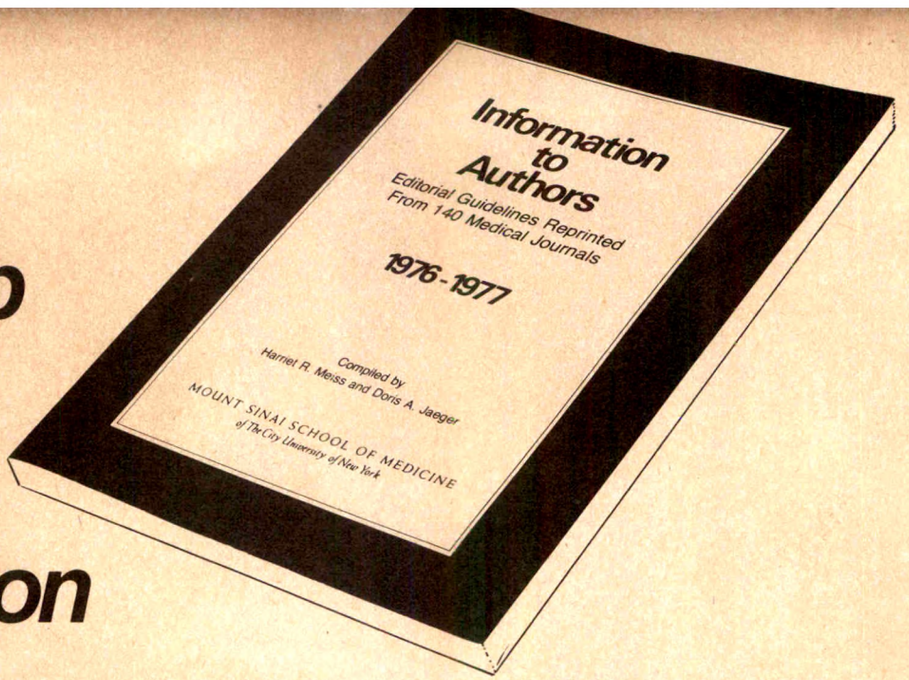

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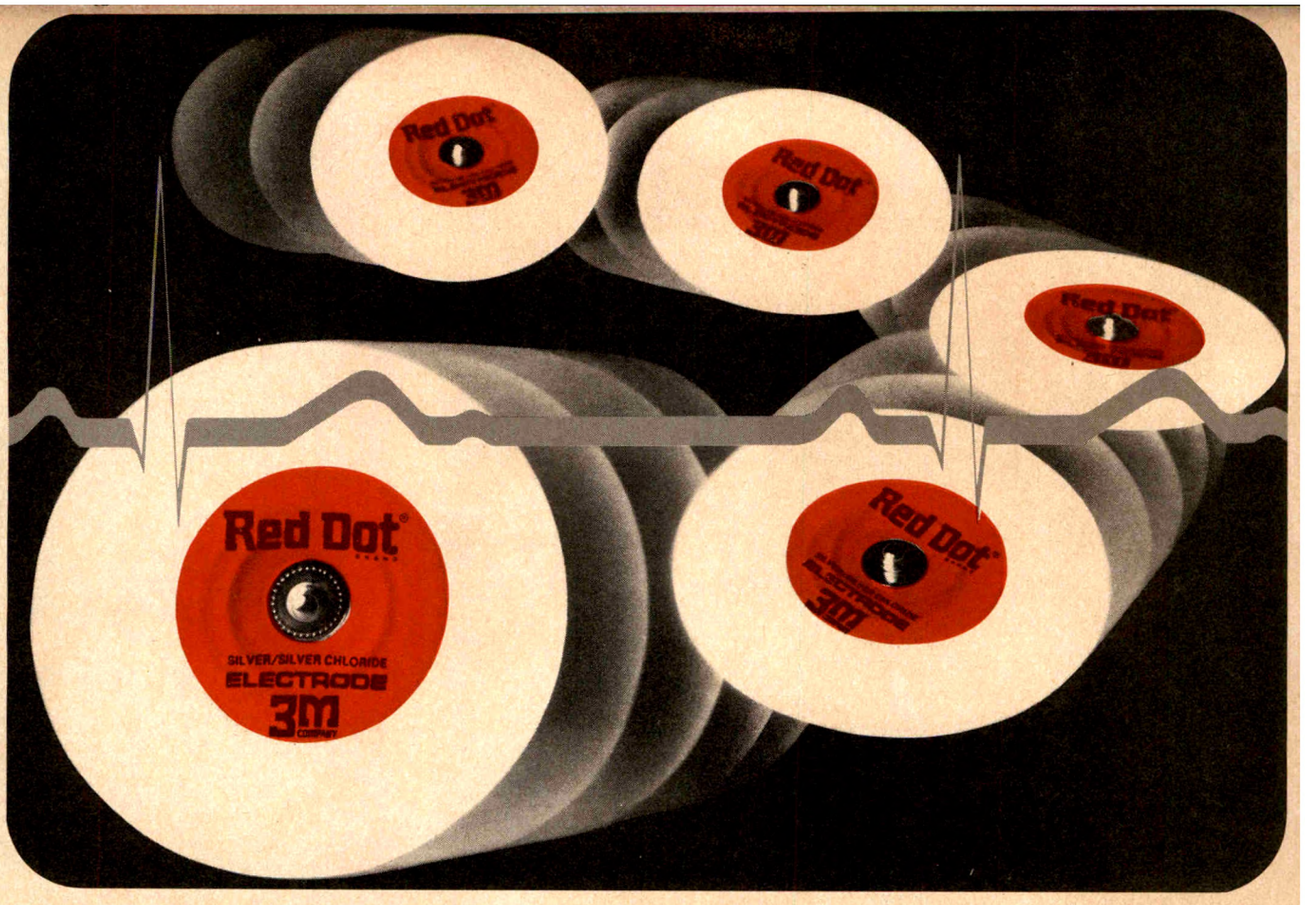

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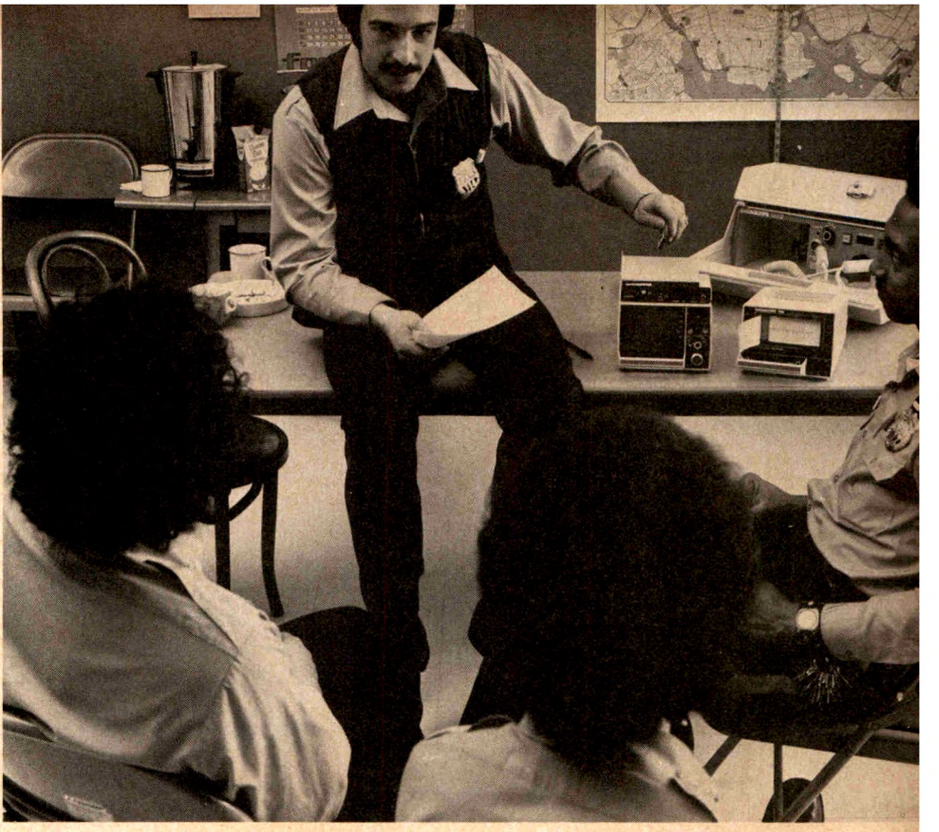

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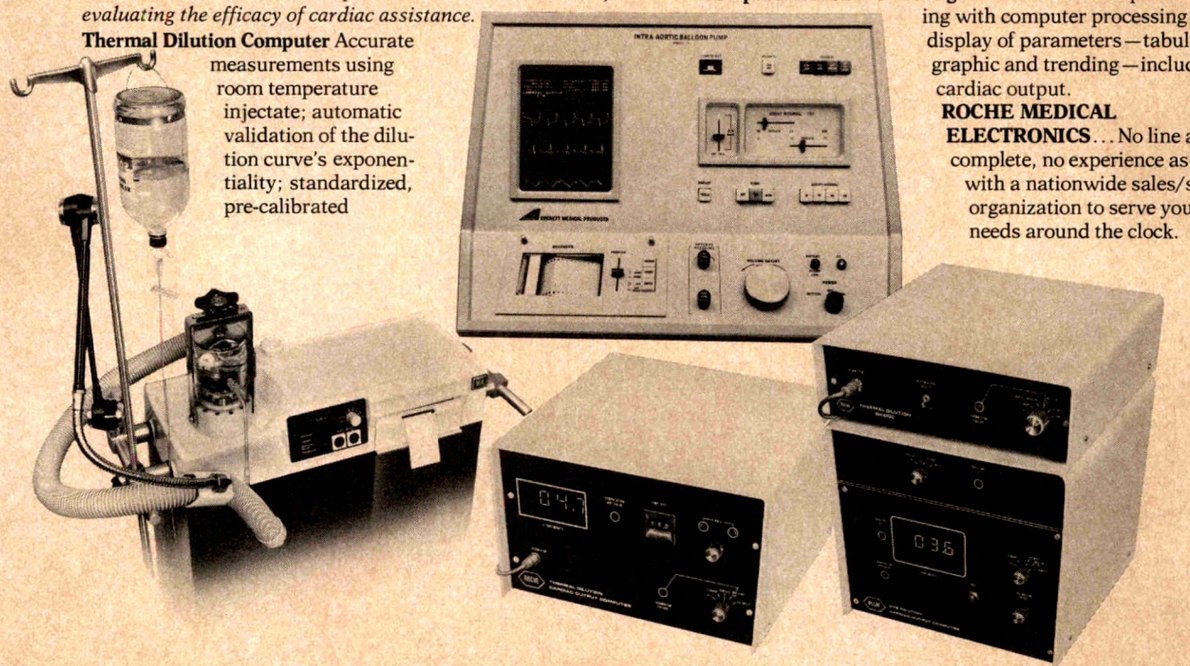

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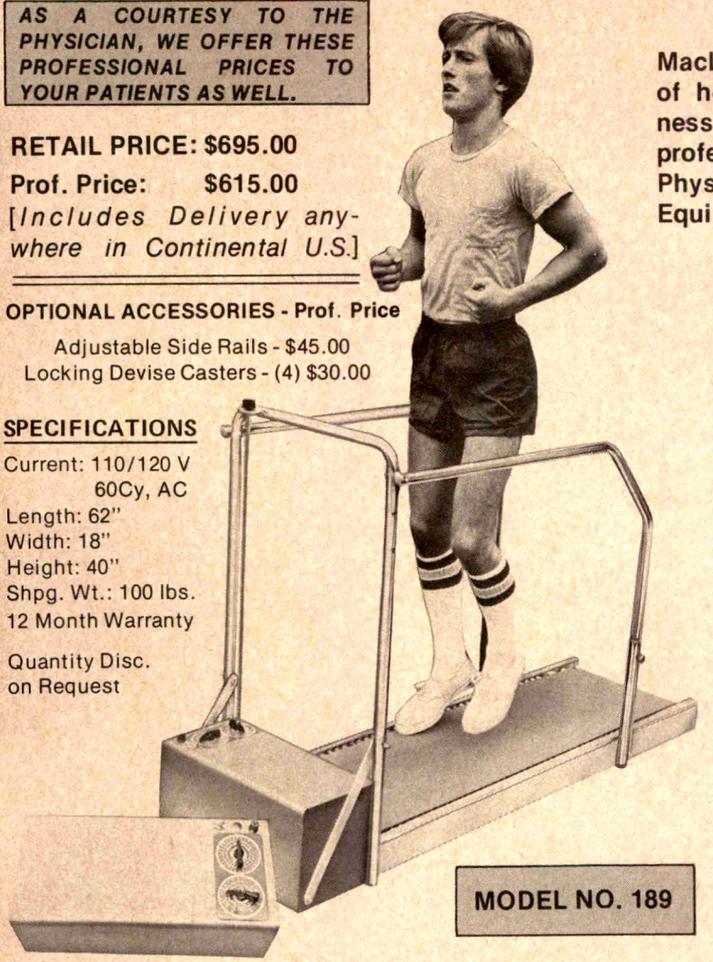

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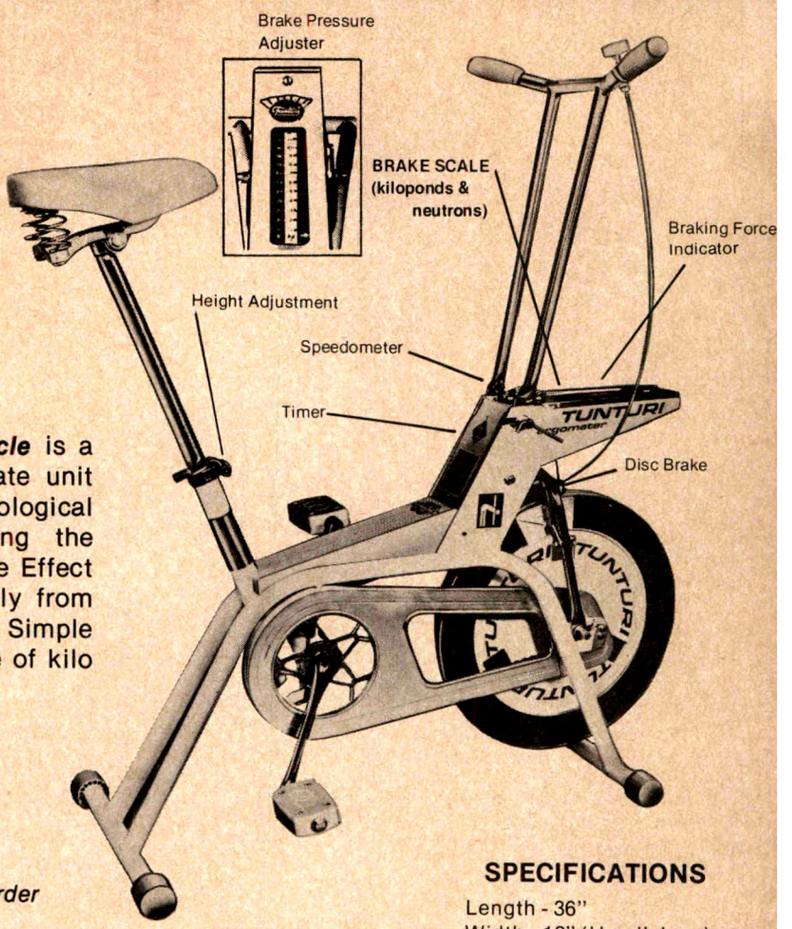

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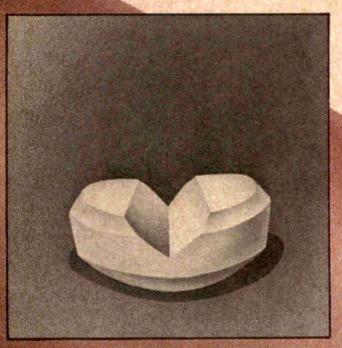

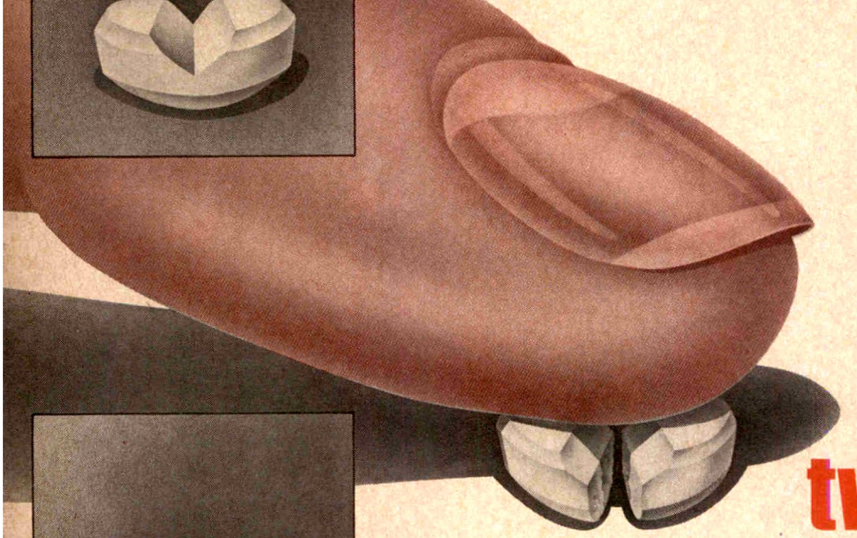

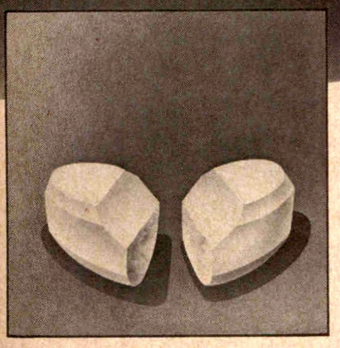

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Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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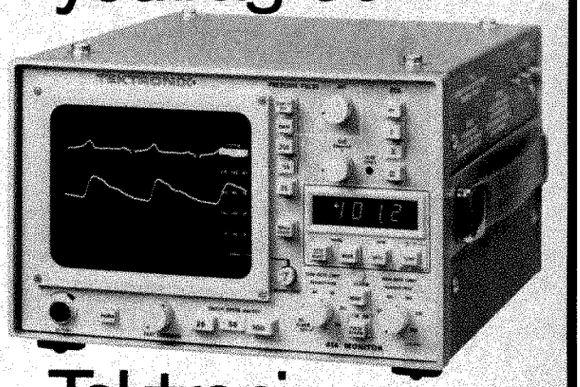

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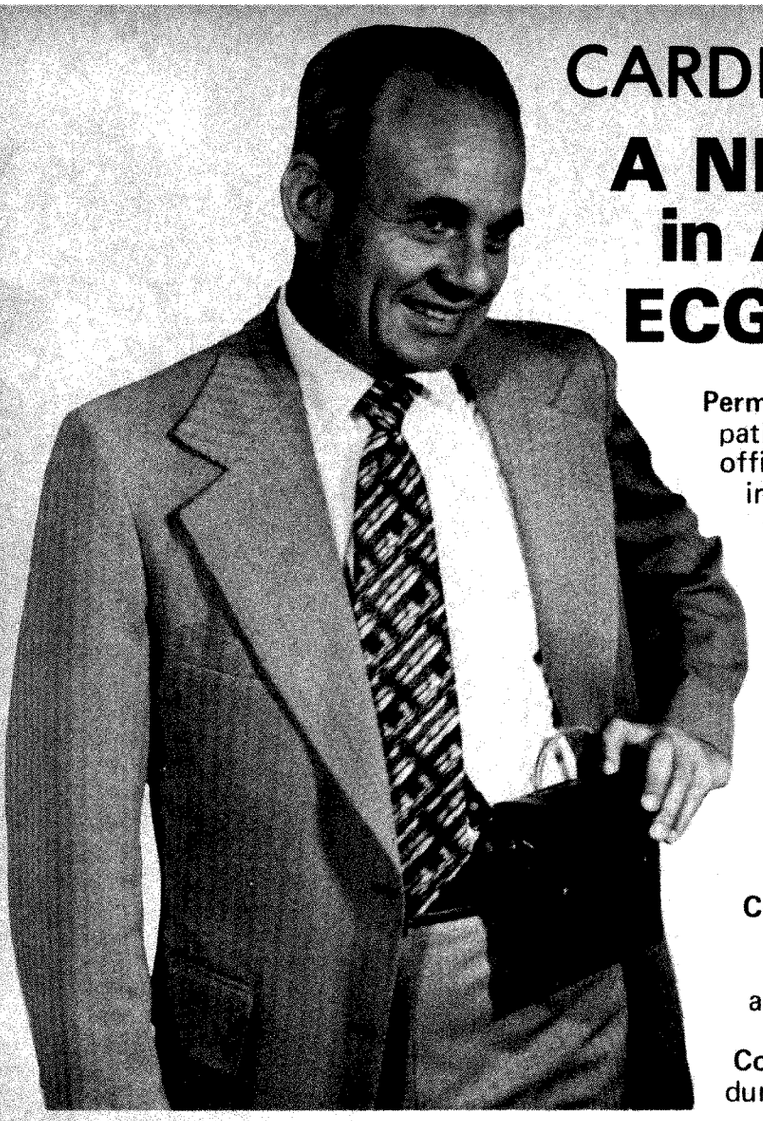

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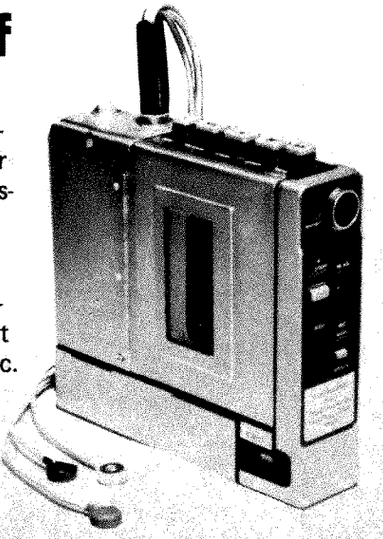

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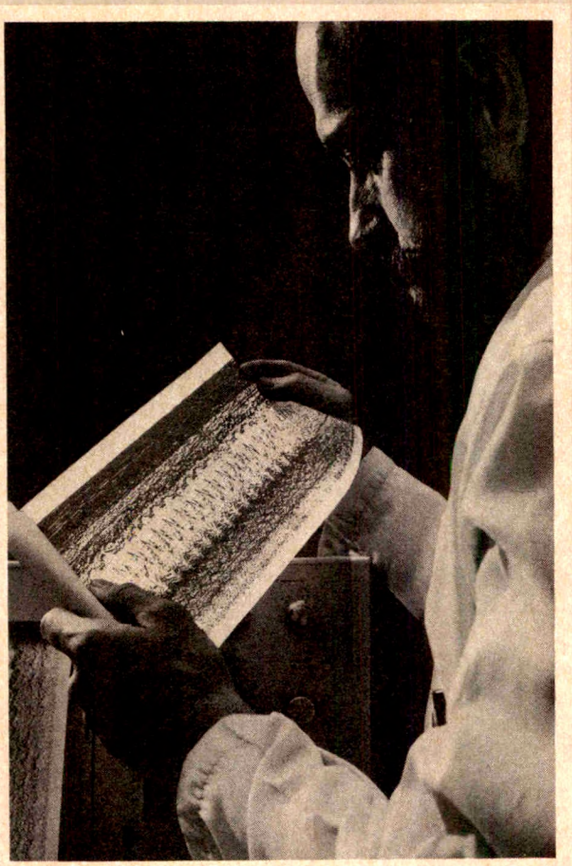

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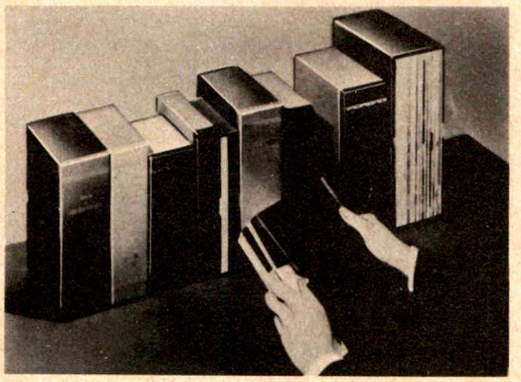

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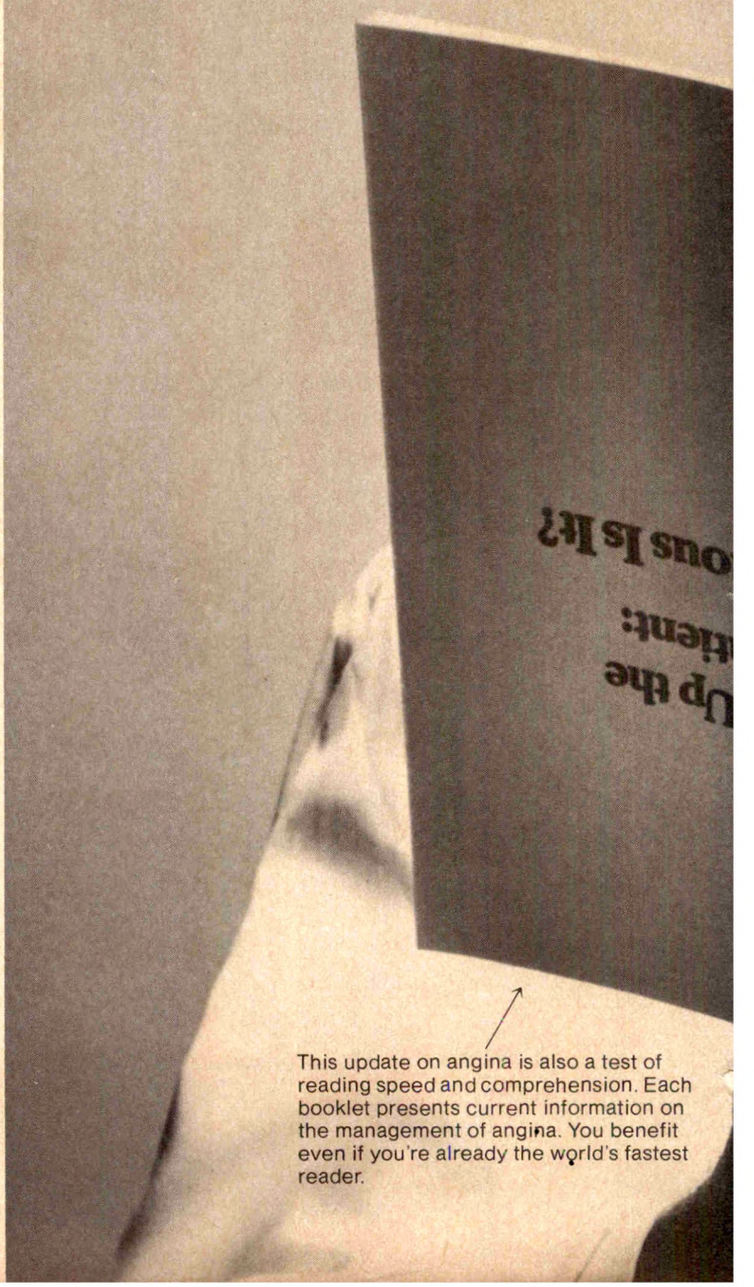

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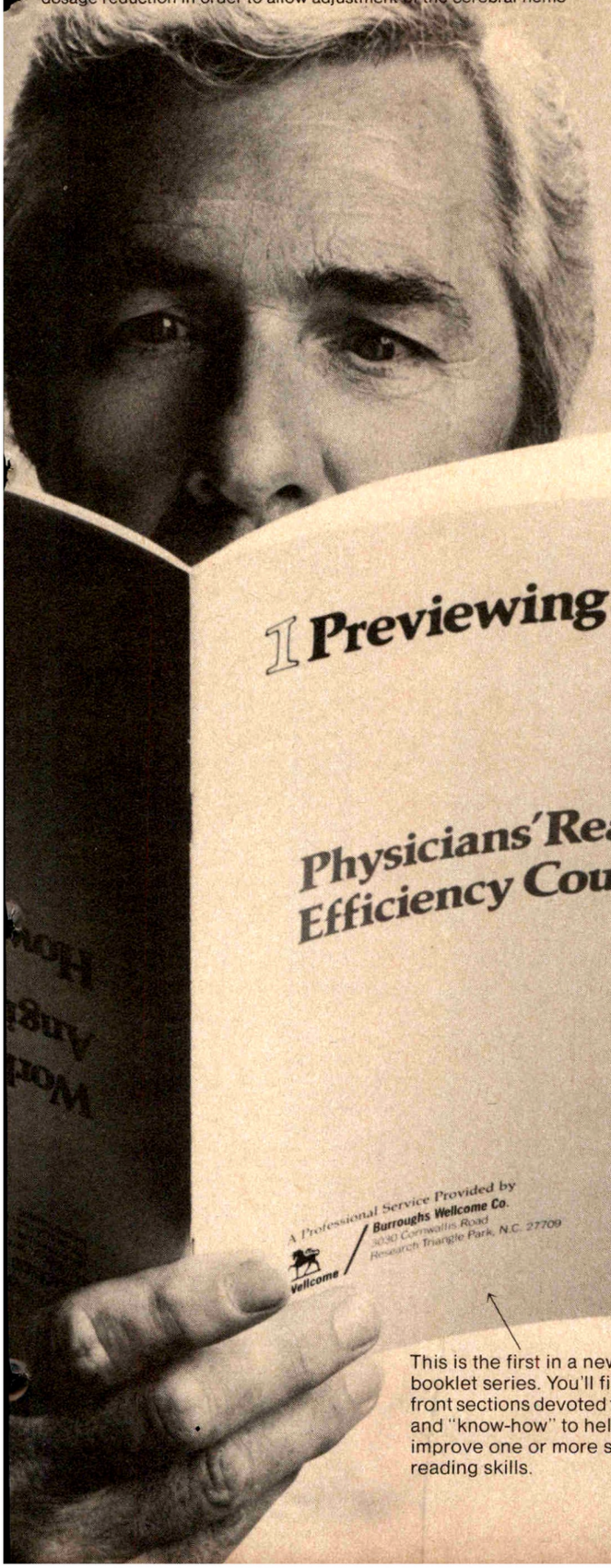

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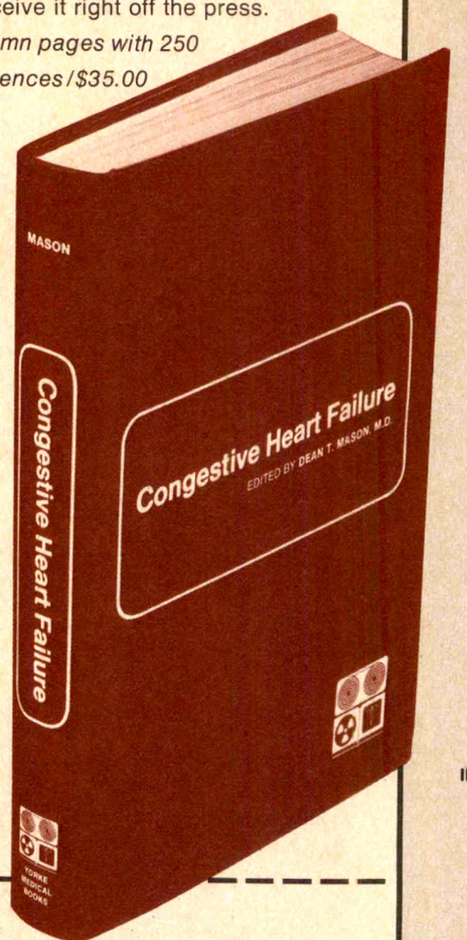

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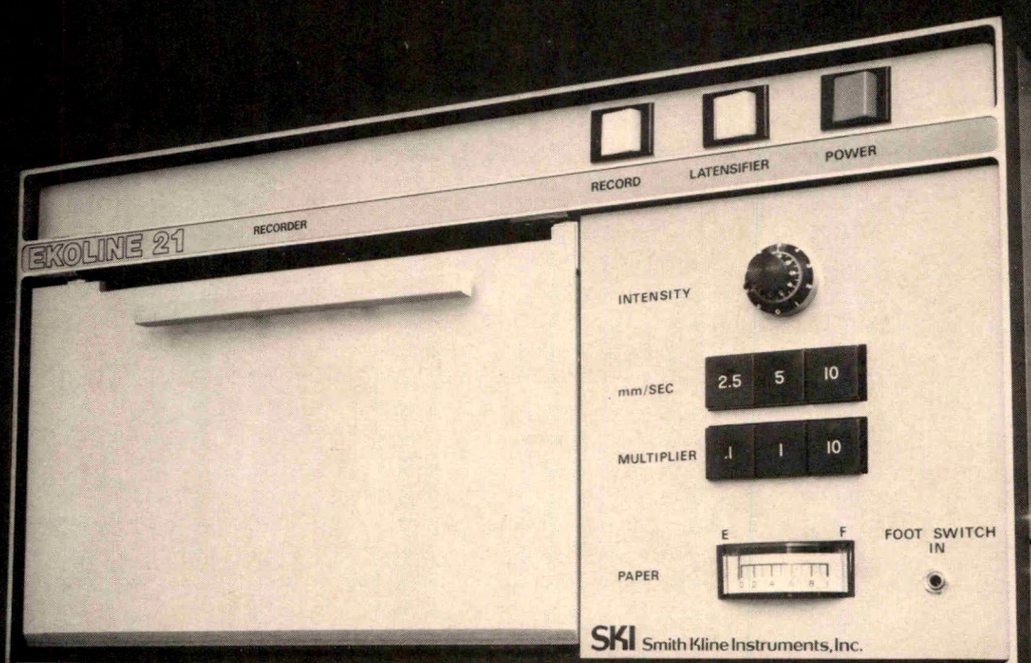

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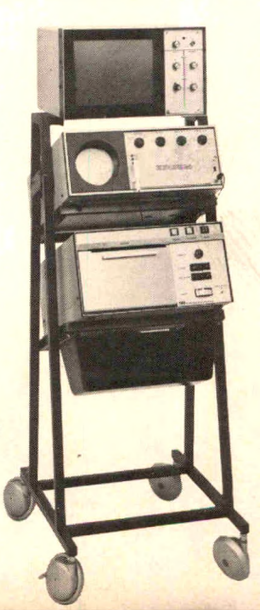

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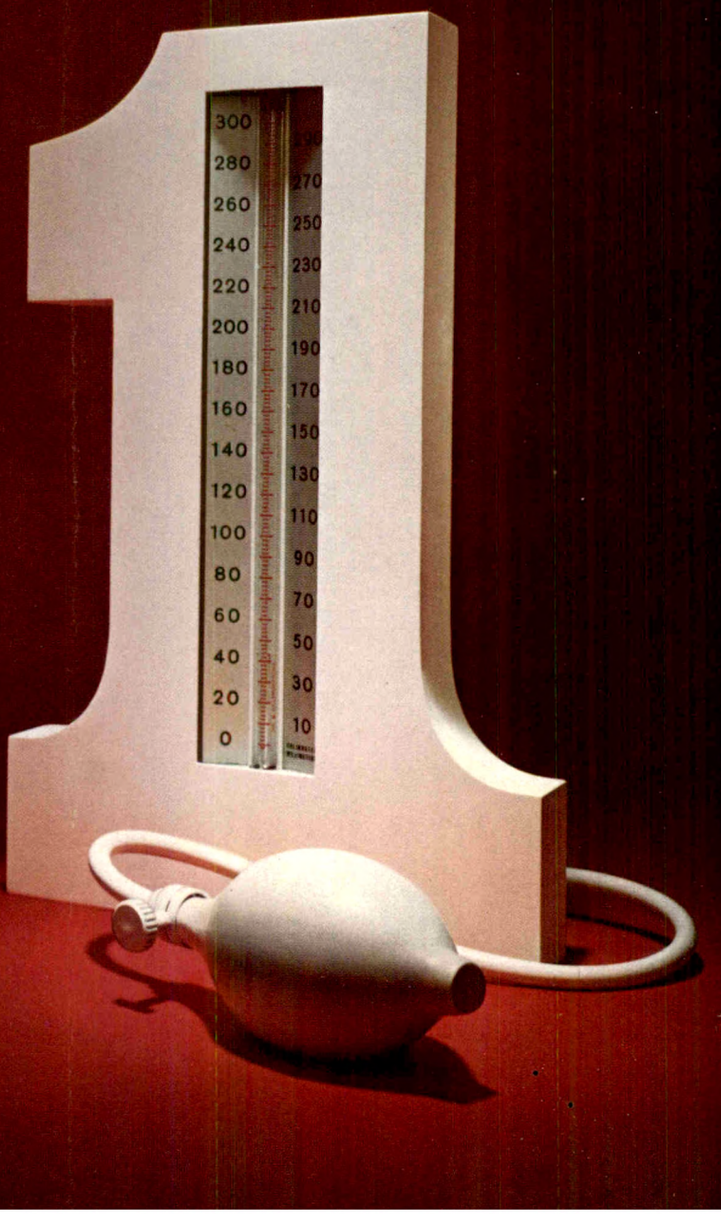

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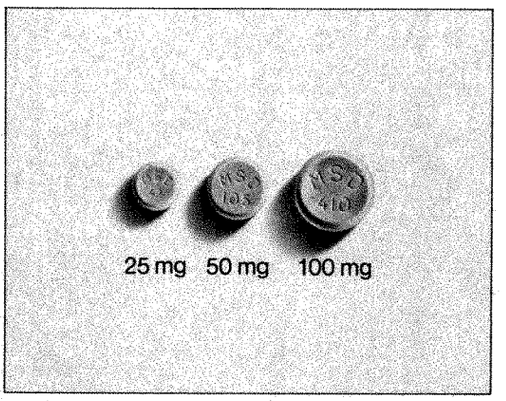

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Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.

Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.

Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.

Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.

Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

How Supplied: Tablets containing 25 mg hydrochlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 50 mg hydrochlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100; Tablets containing 100 mg hydrochlorothiazide each in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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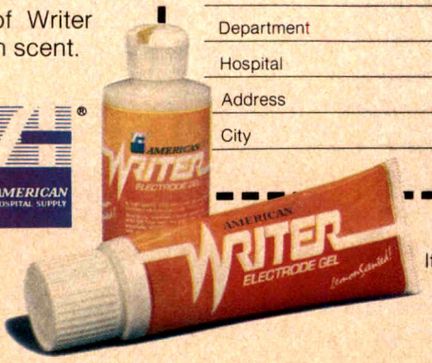

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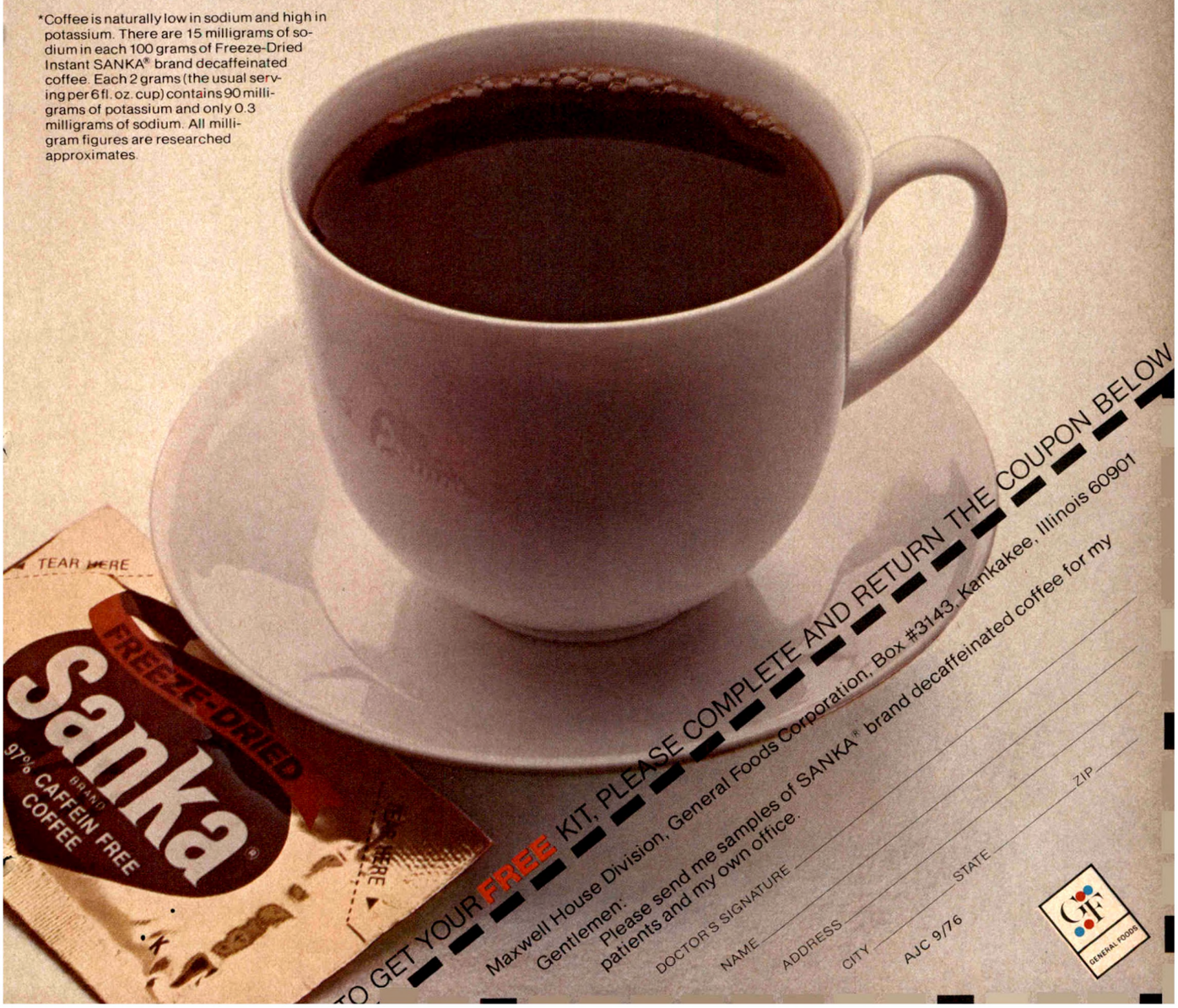

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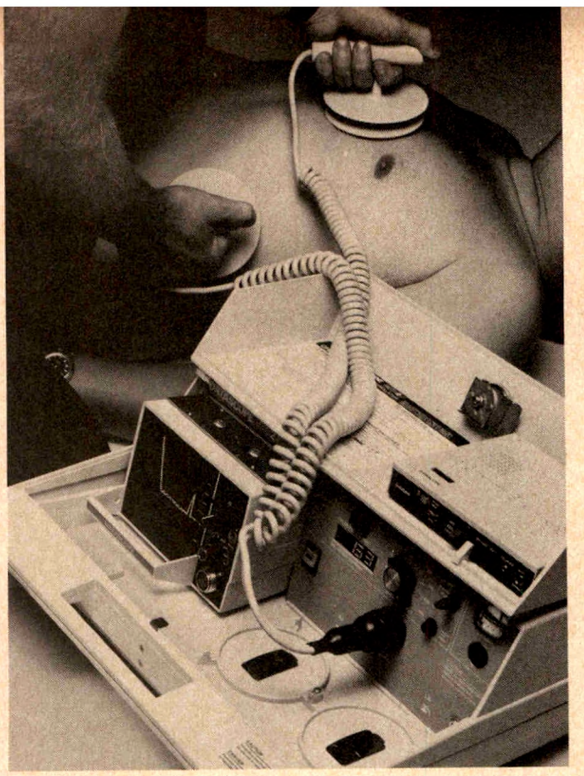

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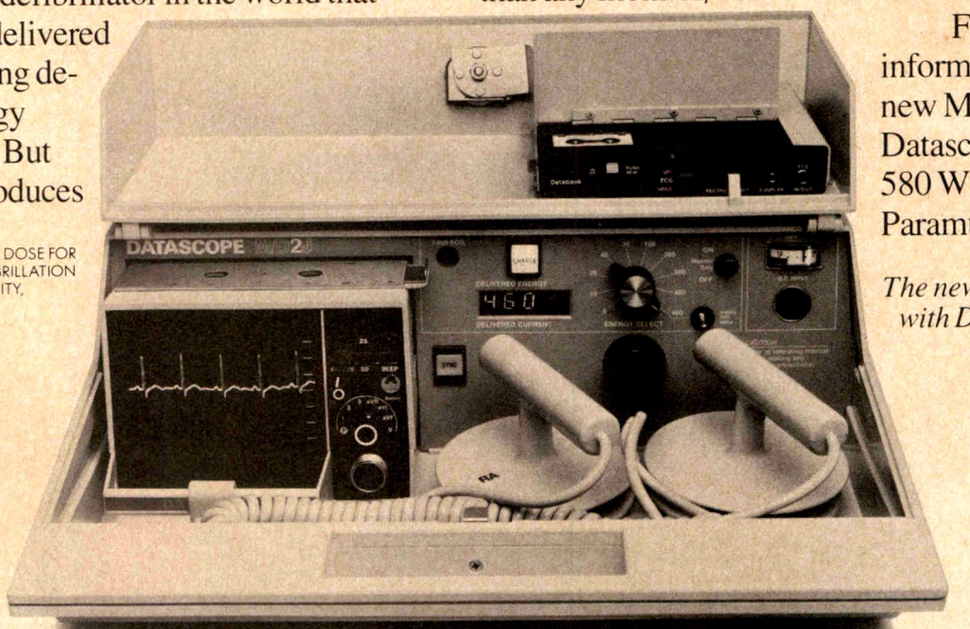

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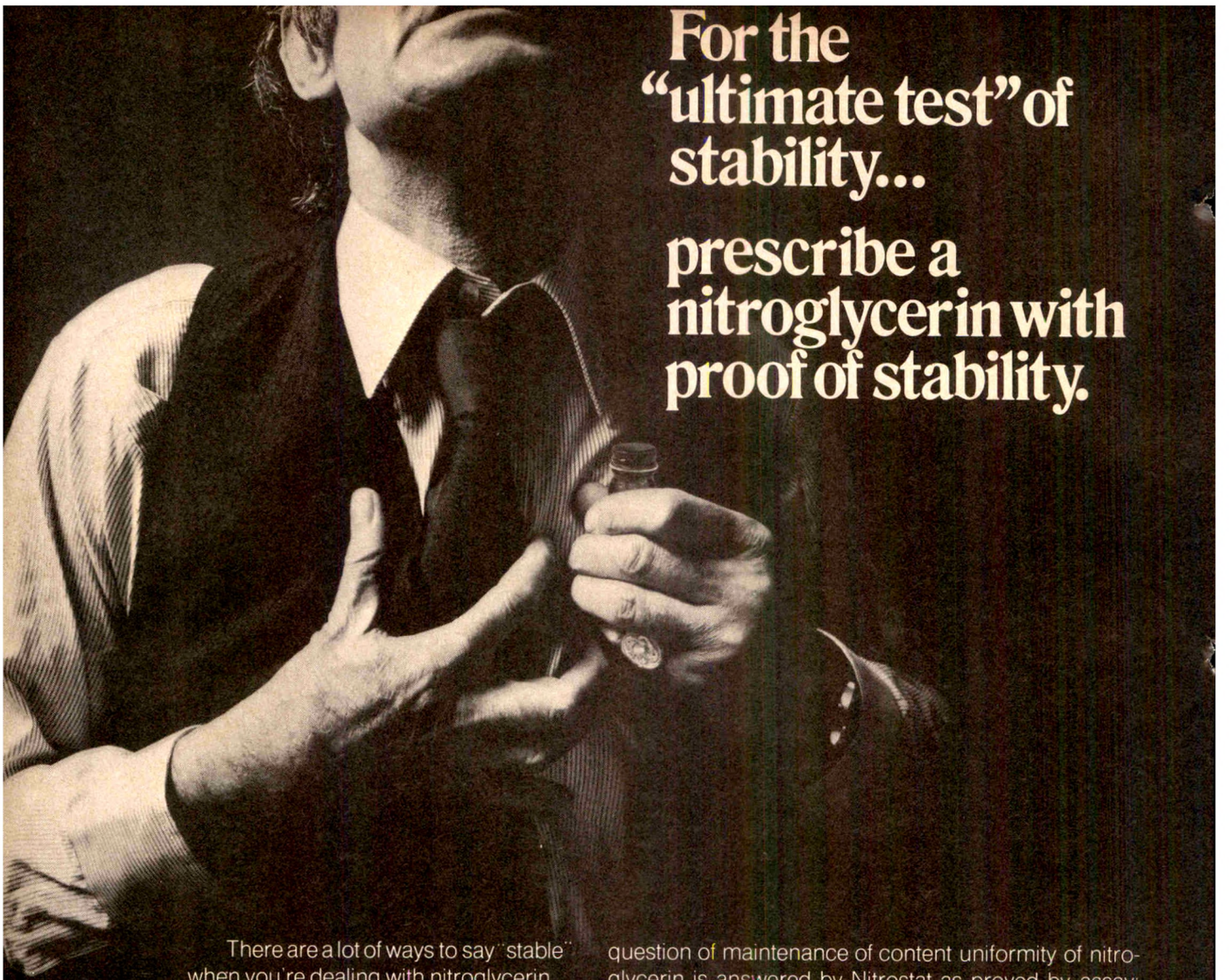

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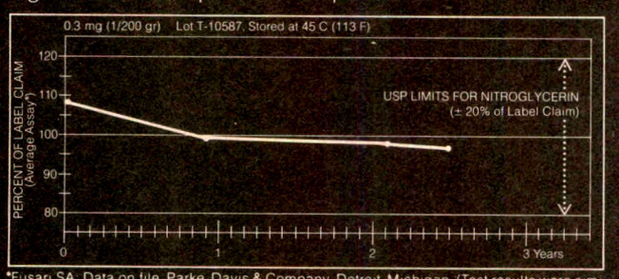

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Observations in 22 patients with prosthetic valve endocarditis and in 74 patients with active infective endocarditis involving natural left-sided cardiac valves revealed significant differences in the percent of ring abscess, hemodynamic consequence, staphylococcus infection, complete heart block or left bundle branch block, but not in age, sex, type of valve disease, frequency of organ infarct or splenomegaly. Regurgitation was the predominant valve dysfunction in aortic prosthetic endocarditis whereas obstruction was the predominant lesion in mitral prosthetic endocarditis.

293 Echocardiogram of the Porcine Aortic Bioprosthesis in the Mitral Position

WINSTON N. BLOCH, JOEL M. FELNER, CHARLES WICKLIFFE, PANAGIOTUS S. SYMBAS and ROBERT C. SCHLANT

These echocardiographic studies demonstrate the usefulness of evaluating the porcine aortic bioprosthesis in the mitral position in 10 consecutive patients. In one patient the combination of absent leaflet echoes and dense nonhomogeneous echoes from the stent on repeated examinations suggested abnormal material such as thrombus within the stent, and at operation a mobile thrombus was found protruding from the atrial side of the valve.

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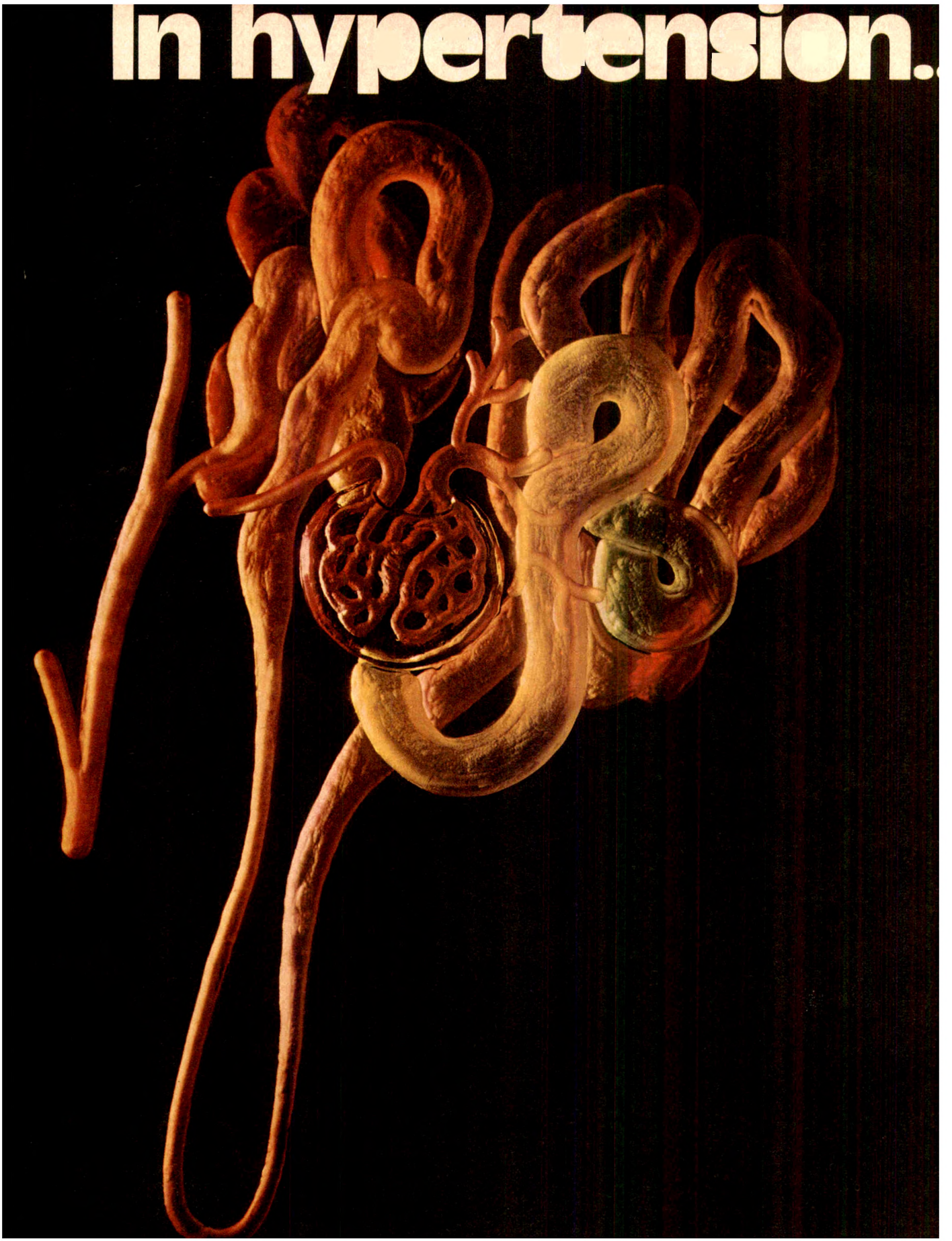
In hypertension..



Hygroton® 50 mg.
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Diuretics reduce blood pressure by blocking sodium retention to lower "effective" volume. But the body's renal compensatory mechanisms are mobilized to promote a secondary sodium conservation, expand "effective" volume and perhaps reelevate blood pressure. Sustained control of "effective" volume is therefore essential to treatment. No other diuretic blocks sodium retention longer than Hygroton.

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BRIEF SUMMARY
Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone; routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May be additive or potentiative of the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Usage in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in cord blood and breast milk. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6.

IN PREDICTABLE ANGINA*

...during episodes of emotional stress

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classifications of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

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Duration of Effect: One to two hours.

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UP TO 2 HOURS OF ANGINA PROTECTION. AT MEALTIME...AND ANY OTHER TIME OF STRESS.

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CONTENTS

299 Myocardial Infarction in Young Women

DOUGLAS C. MORRIS, J. WILLIS HURST and R. BRUCE LOGUE

In this study of 24 women with myocardial infarction under age 40 years, coronary atherosclerosis was the cause in 20 and a nonatherosclerotic coronary occlusive process in 4, including 2 with coronary embolism, and 1 each with lupus erythymatosus and coronary dissection. One or more significant risk factors could usually but not always be documented in the patients with coronary atherosclerosis. The clinical presentation of myocardial ischemia was similar to that seen in the population as a whole.

305 Reappraisal of the Functional Significance of the Coronary Collateral Circulation

ROBERT I. HAMBY, AGOP AINTABLIAN and ANDREW SCHWARTZ

Among the 465 patients with complete obstruction of the left anterior descending or right coronary artery there was a significantly greater frequency of congestive heart failure, cardiomegaly, electrocardiographic evidence of an anterior wall myocardial infarction and angiographic findings of anterior wall asynergy in those with obstruction of the left anterior descending artery (127 patients) without collateral vessels. The evidence indicates that collateral circulation plays a significant protective role in the presence of obstruction of the left anterior descending but not of the right coronary artery.

EXPERIMENTAL STUDIES

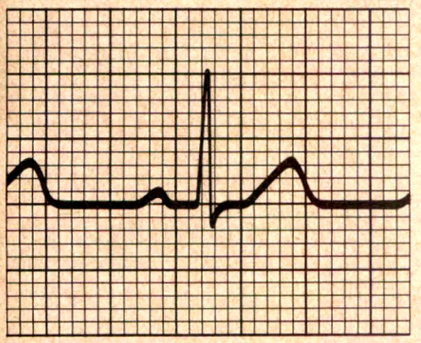
310 Effect of Glucose-Insulin-Potassium Infusions on Arteriovenous Differences of Glucose and of Free Fatty Acids and on Tissue Metabolic Changes in Dogs With Developing Myocardial Infarction

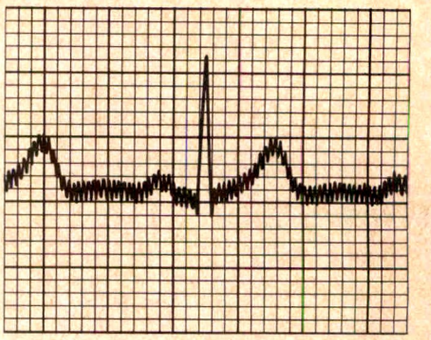
LIONEL H. OPIE

This study confirms previously reported benefits of glucose-insulin-potassium solution on developing myocardial infarction in the dog and baboon. Such solutions given to dogs for 6 hours, starting 30 minutes after ligation of the left anterior descending coronary artery, increased the arteriovenous difference of glucose, decreased that of free fatty acid, decreased the arterial free fatty acid/albumin molar ratio and caused other apparently beneficial changes in the peripheral infarct zone and particularly in the periinfarct zone. The mechanisms of beneficial action may be decreased extraction of free fatty acid by the heart, increased tissue glycogen and a membrane effect.

Continued on page A19

How Burdick separates fact from artifact





A stereo with the high-frequency range to tweet the piccolos and the low-frequency response to boom the cannons of "The 1812 Overture" will also hiss the dust of the record. Similarly, an electrocardiograph, such as the Burdick EK-5A, that's hi-fi enough to register minute voltages important to accurate diagnosis, will also register subtle interference, or artifact.

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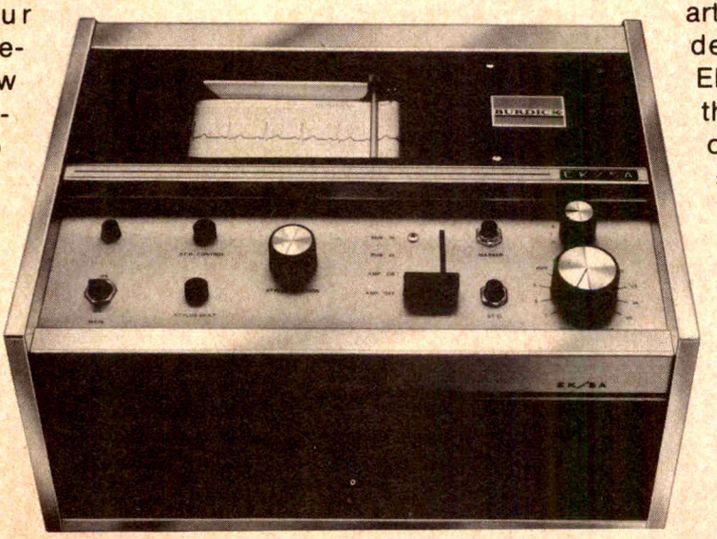

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METHODS

322 Analysis of Wall Dynamics and Directional Components of Left Ventricular Contraction in Man

K. LANCE GOULD, J. WARD KENNEDY, MORRIS FRIMER, GERALD H. POLLACK and HAROLD T. DODGE

Employing a theoretical basis and method and ventricular angiograms to quantify the wall dynamics and directional components of left ventricular contraction in man, these investigators found that left ventricular contraction, quantified separately from inward wall displacement due to mid-wall circumferential shortening, accounted for nearly half of segmental left ventricular work and power. The rate and extent of ventricular thickening correlated closely with ejection fraction and with velocity of circumferential shortening. This method allowed separation of normal and abnormal ventricles and quantification of ventricular performance in 122 patients with valvular, coronary and primary myocardial disease.

STUDIES IN HYPERTENSION

332 Control of Cardiac Output in Essential Hypertension

MICHEL E. SAFAR, NGUYEN P. CHAU, YVES A. WEISS, GÉRARD M. LONDON and PAUL L. MILLIEZ

This study of 101 normotensive and 101 hypertensive men of the same age points to the role of a functional renal abnormality in maintaining normal cardiac output in patients with essential hypertension. The volume and neural control of blood pressure are disrupted in hypertension whereas control of cardiac output is maintained. Adaptive mechanisms involving renal function are necessary for the maintenance of normal cardiac output in patients with essential hypertension.

PEDIATRIC CARDIOLOGY

337 Echocardiographic Spectrum of the Hypoplastic Left Heart Syndrome

ZIA Q. FAROOKI, JAMES G. HENRY and EDWARD W. GREEN

Echocardiography proved safe and reliable in delineating the intracardiac anatomy in 19 sick neonates with the hypoplastic left heart syndrome, and was particularly valuable in those with shock. The diagnostic echocardiographic features included (1) a left ventricular end-diastolic dimension of less than 9 mm, (2) an aortic root diameter of less than 6 mm, (3) a left ventricular end-diastolic/right ventricular end-diastolic dimension ratio of less than 0.6 and (4) an absent or greatly distorted mitral valve echo of small amplitude.

Continued on page A21

IN CARDIAC OR CEREBROVASCULAR DISEASE

where straining at stool may be hazardous

Effectively help avoid straining

Clinicians have recommended that SENOKOT laxatives be used routinely to *avoid* constipation in cardiac patients, as a possible means of reducing deaths and accidents due to straining at stool.[1] Routine use of SENOKOT laxatives for cerebrovascular patients has also helped prevent effects of excessive straining which may lead to transient cerebral ischemia in the elderly.[2]

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References: 1. McGuire, J., *et al,* cited in Exton-Smith, A. Norman: Constipation in Geriatrics, in *Management of Constipation,* edited by Sir Francis Avery Jones and Edmund W. Godding, Oxford, Blackwell Scientific Publications, 1972, p. 162. **2.** Halpern, A., *et al,* cited in Exton-Smith, A. Norman, *ibid.* **3.** Godding, E. W.: Therapeutic Agents, in *Management of Constipation, op cit* (ref. 1), p. 65.

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(standardized senna concentrate)

a natural vegetable laxative

Senokot laxative claims are documented

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344 **Surgical Correction in Complete Levotransposition of the Great Arteries With an Unusual Subaortic Ventricular Septal Defect**

CHRISTOPHER LINCOLN, JOACHIM HASSE, ROBERT H. ANDERSON and ELLIOT SHINEBOURNE

The clinical, angiographic and surgical features of six children with this variant of complete levotransposition of the great vessels are reported. All had successful surgical correction. The significance of the cases is discussed in relation to terminology, classification and morphogenesis of this variant of transposition.

352 **Asymmetric Distribution of the Pulmonary Blood Flow Between the Right and Left Lungs in *d*-Transposition of the Great Arteries**

ALEXANDER J. MUSTER, MILTON H. PAUL, ALBERTUS VAN GRONDELLE and JAMES J. CONWAY

Approximately 50 percent of 63 patients with *d*-transposition of the great arteries showed greater perfusion of the right than of the left lung in an evaluation by pulmonary angiograms, radionuclide lung images and chest roentgenograms. The pattern of blood flow correlated well with the angulation between the main and right pulmonary arteries and was influenced by additional pulmonary stenosis, which increased the disparity in perfusion. The disparity in perfusion increases with time and may result in cessation of perfusion to the left lung.

REVIEW

362 **Limitations of the Computer in Electrocardiographic Interpretation**

CESAR A. CACERES

Although computers have been increasingly used to interpret electrocardiograms over the past 10 years, lack of sufficient objectivity in clinical electrocardiographic criteria for measurement and diagnosis have hampered their general acceptance. This excellent review summarizes the available computer programs, their advantages and their limitations. Awareness of the limits of computer performance allows its proper application to clinical electrocardiographic practice.

Continued on page A23

The patient with cardiac arrhythmia may need medication most when he's least likely to take it...

while he's sleeping.

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- produces sustained serum quinidine levels, thus providing a convenient 8 or 12 hour dosage schedule
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Contraindications: Quinaglute Dura-Tabs are contraindicated in patients with partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening; in patients manifesting idiosyncrasy or sensitivity to quinidine (e.g. febrile reactions, skin eruptions, thrombocytopenia, etc.), in patients with renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. It may be contraindicated in certain patients who have marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered; especially during the first weeks of therapy.

Signs of idiosyncrasy include febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment. Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure, with digitalis intoxication, or renal insufficiency. It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

As with all quinidine preparations, the titrating of the exact quinidine dosage will vary with each individual patient. With the dosage regimen of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythm.

As with other quinidine products, Quinaglute Dura-Tabs should not be used during pregnancy.

Adverse Reactions: The patient should be advised to report immediately to the physician any symptoms of cinchonism (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis and respiratory distress).

Where such symptoms develop, or if evidence of hypotension appears, the drug should be discontinued. Gastrointestinal disturbances have only rarely been reported. If they occur, they may be minimized by administering the drug with food. If they persist, dosage should be decreased.

Dosage: For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours.

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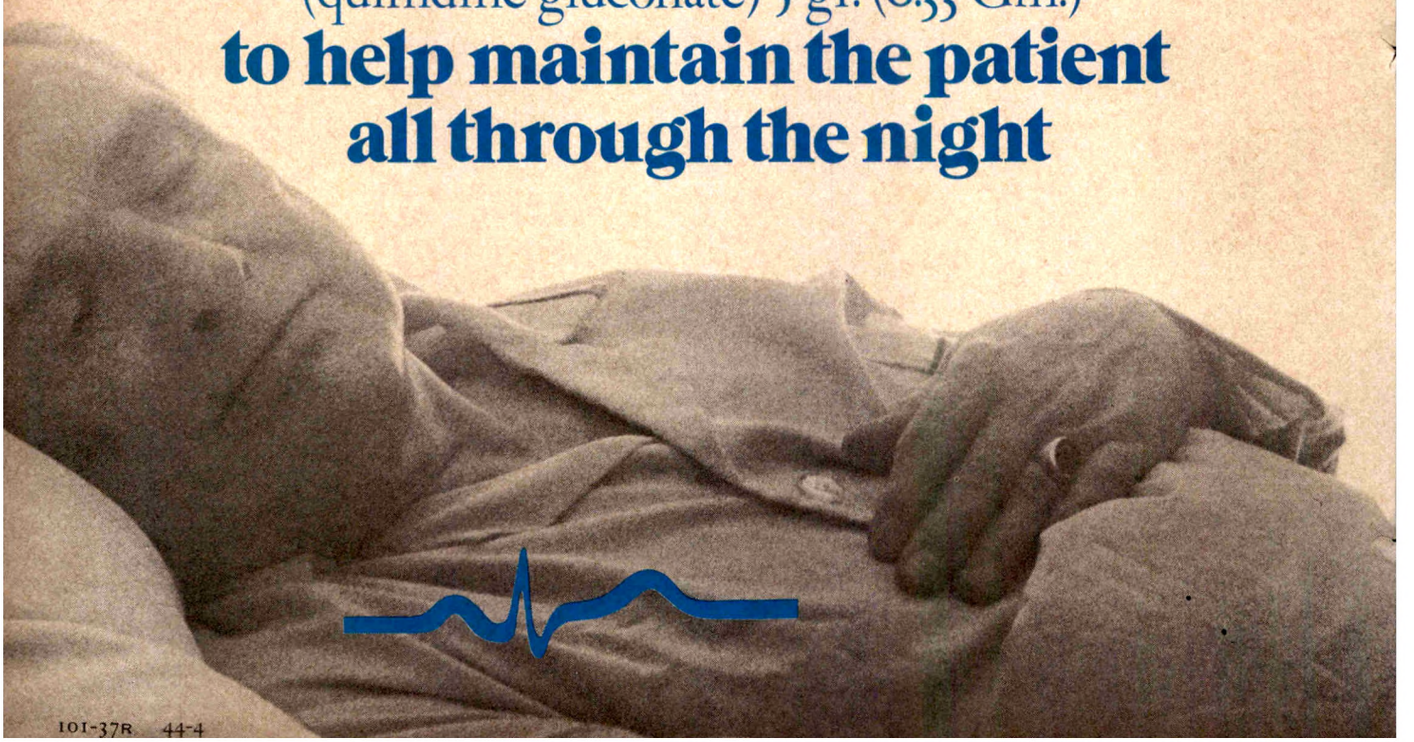

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377 Prolapse of the Mitral Valve (Floppy Valve) Associated With Ebstein's Anomaly of the Tricuspid Valve

WILLIAM C. ROBERTS, D. LUKE GLANCY, RONALD P. SENINGEN, BARRY J. MARON and STEPHEN E. EPSTEIN

This report presents the clinical and postmortem features of a previously undescribed association of a prolapsed mitral valve with Ebstein's anomaly of the tricuspid valve in two women.

383 Congenitally Corrected Transposition of the Great Vessels: Localization of the Site of Complete Atrioventricular Block Using His Bundle Electrograms

JAMES R. FOSTER, ANTHONY N. DAMATO, LAWRENCE E. KLINE, MASOOD AKHTAR and JEREMY N. RUSKIN

His bundle studies disclosed that the spontaneous rhythm originated from the bundle of His in this 20 year old man with congenitally corrected transposition of the great vessels and complete atrioventricular (A-V) block proximal to the bundle of His. The responsiveness of the rate of bundle of His to carotid sinus massage and atropine suggests that vagal maneuvers may fail to differentiate between junctional rhythms of bundle of His and A-V nodal origin.

388 Pathologic Correlations in a Case of Complete Heart Block With Split His Potentials Resulting From a Stab Wound of the Heart

SAROJA BHARATI, WILLIAM D. TOWNE, RAMESH PATEL, MAURICE LEV, SHAHBUDIN H. RAHIMTOOLA and KENNETH M. ROSEN

A stab wound of the heart in a previously well 23 year old man caused a ventricular septal defect and complete atrioventricular block. Despite electrophysiologic evidence of a bifurcation of the bundle of His 26 days after the trauma, postmortem examination three years later showed its total absence, presumably due to fibrosis of the bifurcation produced by hemodynamic changes at the lower margin of the ventricular septal defect.

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CHARLES A. BERTRAND

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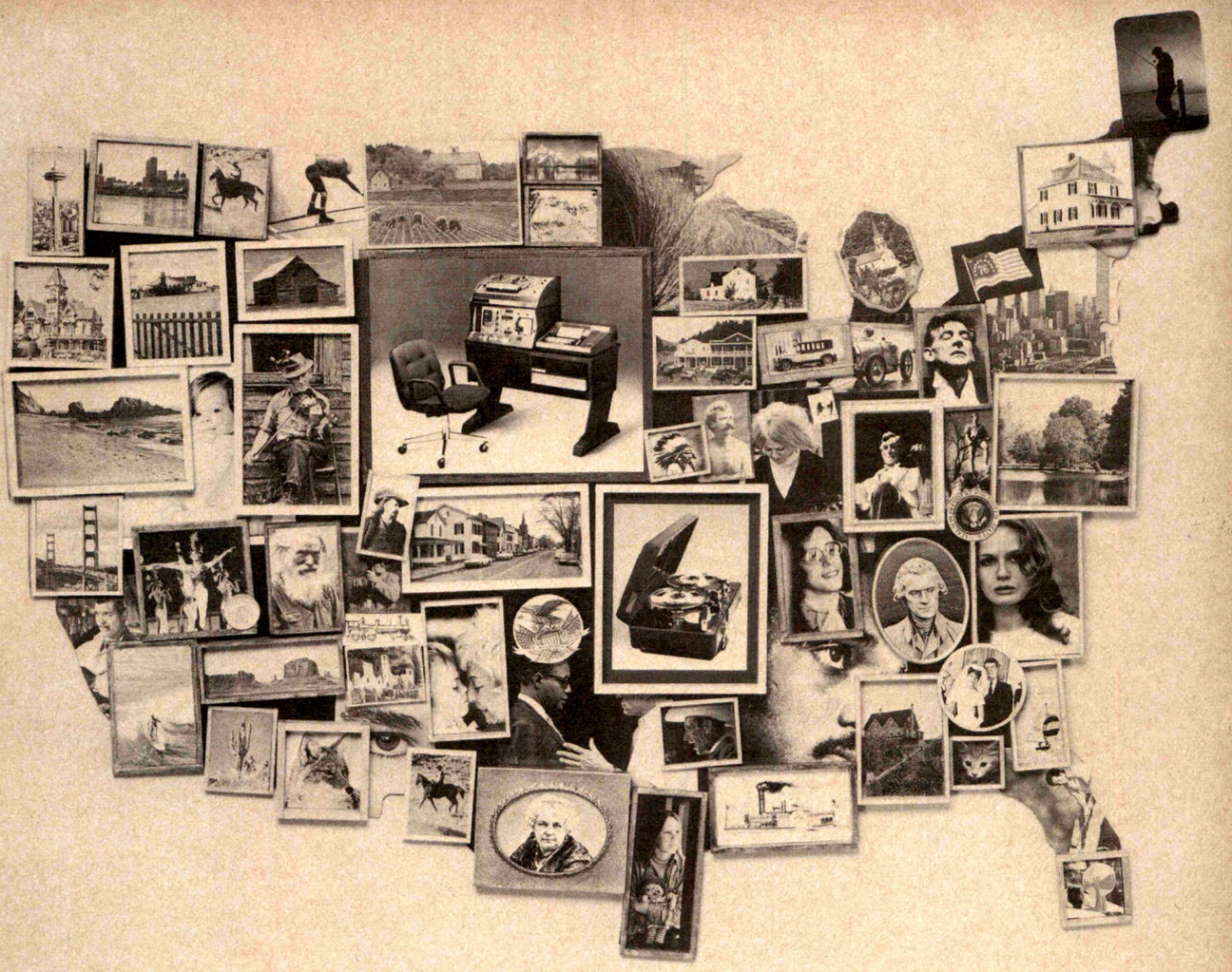

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(pentaerythritol tetranitrate) 80mg

CAUTION: Federal law prohibits dispensing without prescription.

Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Peritrate® (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg (b.i.d. on an empty stomach), 1 tablet immediately on arising and 1 tablet 12 hours later. Tablets should not be chewed.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg, double layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also in unit dose—package of 10 x 10 strips (N 0047-0004-11).

Additional Dosage Forms: Peritrate 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also in unit dose—package of 10 x 10 strips (N 0047-0001-11). Peritrate 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

Full information is available on request.

Defense against attack.
For over 22 years, Peritrate® has been considered by many physicians as one of the top defensive measures for patients with angina pectoris. In many patients Peritrate used prophylactically helps decrease the frequency and severity of angina attacks.* With minimal side effects.
Peritrate can also help reduce nitroglycerin requirements and, therefore, nitroglycerin side effects. Is it any wonder so many physicians continue to prefer Peritrate prophylaxis for their angina patients?
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The Great Wall of China, an immense 1,400-mile-long man made barrier 20 to 30 feet high and 15 to 20 feet thick, helped defend China from the attack of Mongol hordes for more than 2,000 years.
*The drug has been evaluated as possibly effective for this indication.
See brief summary.

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J. Willis Hurst and Dean T. Mason

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Volume II

Edited by ROBERT C. SCHLANT and J. WILLIS HURST

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HYPERSTAT® I.V. (brand of diazoxide, USP) Injection

FOR INTRAVENOUS USE IN HOSPITALIZED PATIENTS ONLY

INDICATIONS For the emergency reduction of blood pressure in malignant hypertension in hospitalized patients, when prompt and urgent decrease of diastolic pressure is required. Treatment with orally effective antihypertensive agents should be instituted as soon as the hypertensive emergency is controlled. HYPERSTAT I.V. Injection is ineffective against hypertension due to pheochromocytoma.

CONTRAINDICATIONS It should not be used in the treatment of compensatory hypertension, such as that associated with aortic coarctation or arteriovenous shunt, nor in patients hypersensitive to diazoxide or other thiazides, unless the potential benefits outweigh the possible risks.

WARNINGS Safety in pregnancy and in children has not yet been established. Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults. Hypotension may occasionally result. If severe enough to require therapy, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine. Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored, especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide. Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. Concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions). Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent. Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

PRECAUTIONS HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available. It should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively. Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response. As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental. Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection. Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

ADVERSE REACTIONS

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by unconsciousness, convulsions, paralysis, confusion or focal neurological deficit, such as numbness of the hands; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions, such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported. Papilledema, induced by plasma volume expansion secondary to the administration of diazoxide, was reported in one patient who had received eleven injections over a twenty-two day period.

Other adverse reactions: Vasodilative phenomena, such as orthostatic hypotension, sweating, flushing, and generalized or localized sensations of warmth; supraventricular tachycardia and palpitation; bradycardia; various transient neurological findings secondary to alterations in regional blood flow to the brain, such as headache (sometimes throbbing), dizziness, lightheadedness, sleepiness (also reported as lethargy, somnolence or drowsiness), euphoria or "funny feeling", ringing in the ears and momentary hearing loss, and weakness of short duration; chest discomfort or nonanginal "tightness in the chest"; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; and various respiratory and gastrointestinal findings, secondary to the relaxation of smooth muscle, such as dyspnea, cough and choking sensation; nausea and vomiting and/or abdominal discomfort, anorexia, alteration in taste, parotid swelling, salivation, dry mouth, lacrimation, ileus, constipation and diarrhea. Also, warmth or pain along the injected vein; cellulitus without sloughing and/or phlebitis at the site of extravasation; back pain; and increased nocturia. Apprehension or anxiety, malaise and blurred vision occurred on single occasions.

DRUG INTERACTIONS Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

OVERDOSAGE Overdosage may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agent suggests that the hypotension may have been caused by something other than diazoxide. Excessive hyperglycemia resulting from overdosage will respond to conventional therapy of hyperglycemia. Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

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Effective, Convenient Stat Regimen–for rapid reduction of blood pressure in malignant hypertension

direct-action

Hyperstat® I.V.

Brand of DIAZOXIDE

INJECTION
20 ml ampule
contains 300 mg

"The injection of the [diazoxide] bolus in 10 to 15 seconds results in a prompt blood pressure fall in a high percentage of cases. A maximal blood pressure response usually occurs within 5 to 10 minutes."*

☐ **Rapid reduction to normotensive levels**

Induces rapid reduction of blood pressure generally within 5 minutes...often in 1 or 2 minutes to the lowest level achieved. Blood pressure response facilitated by appropriate diuretic therapy.

☐ **Prolonged activity**

A single injection of HYPERSTAT I.V. generally maintains blood pressure below pretreatment levels for periods up to 12 hours.

☐ **Protective action—helps avert target organ damage**

Cardiac output increases as diastolic pressure is reduced. Coronary and cerebral blood flow maintained. Increased renal blood flow after transient decrease.

☐ **Uncomplicated procedure**

Simple I.V. "push" in a peripheral vein in 30 seconds or less. Close monitoring at frequent intervals is necessary until blood pressure is stabilized (generally 15-30 minutes). Thereafter, hourly measurement should be taken during the balance of effect.

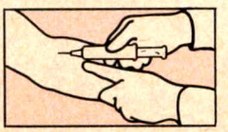
☐ **Convenient...no preparation**

HYPERSTAT I.V. supplied as a 20 ml ampule containing 300 mg diazoxide in ready to use solution.

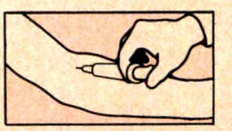
*Marvin Moser, M.D., Assistant Professor of Clinical Medicine, Albert Einstein College of Medicine, and Chief of Cardiology, White Plains Hospital, White Plains, N.Y., in Diazoxide—an effective vasodilator in accelerated hypertension. *Am Heart J* 87(6): 791-795, June 1974.

Administration guidelines

1. Fill dry syringe with appropriate dose of HYPERSTAT I.V. Injection (20 ml ampule contains 300 mg diazoxide).



2. Hospitalized patient should be recumbent. Insert needle only into a peripheral vein.



3. Inject entire dose I.V. in 30 seconds or less. Remove needle carefully—avoid extravasation.

4. Keep patient recumbent for at least half an hour after injection; monitor BP closely until stabilized—usually 15-30 minutes.

5. If patient is to be ambulatory, measure BP in standing position before ending surveillance.

6. HYPERSTAT I.V. Injection should be continued until a regimen of oral antihypertensive medication becomes effective (generally within a few days).

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Before prescribing HYPERSTAT I.V. Injection, please consult complete product information, a summary of which appears on the facing page.

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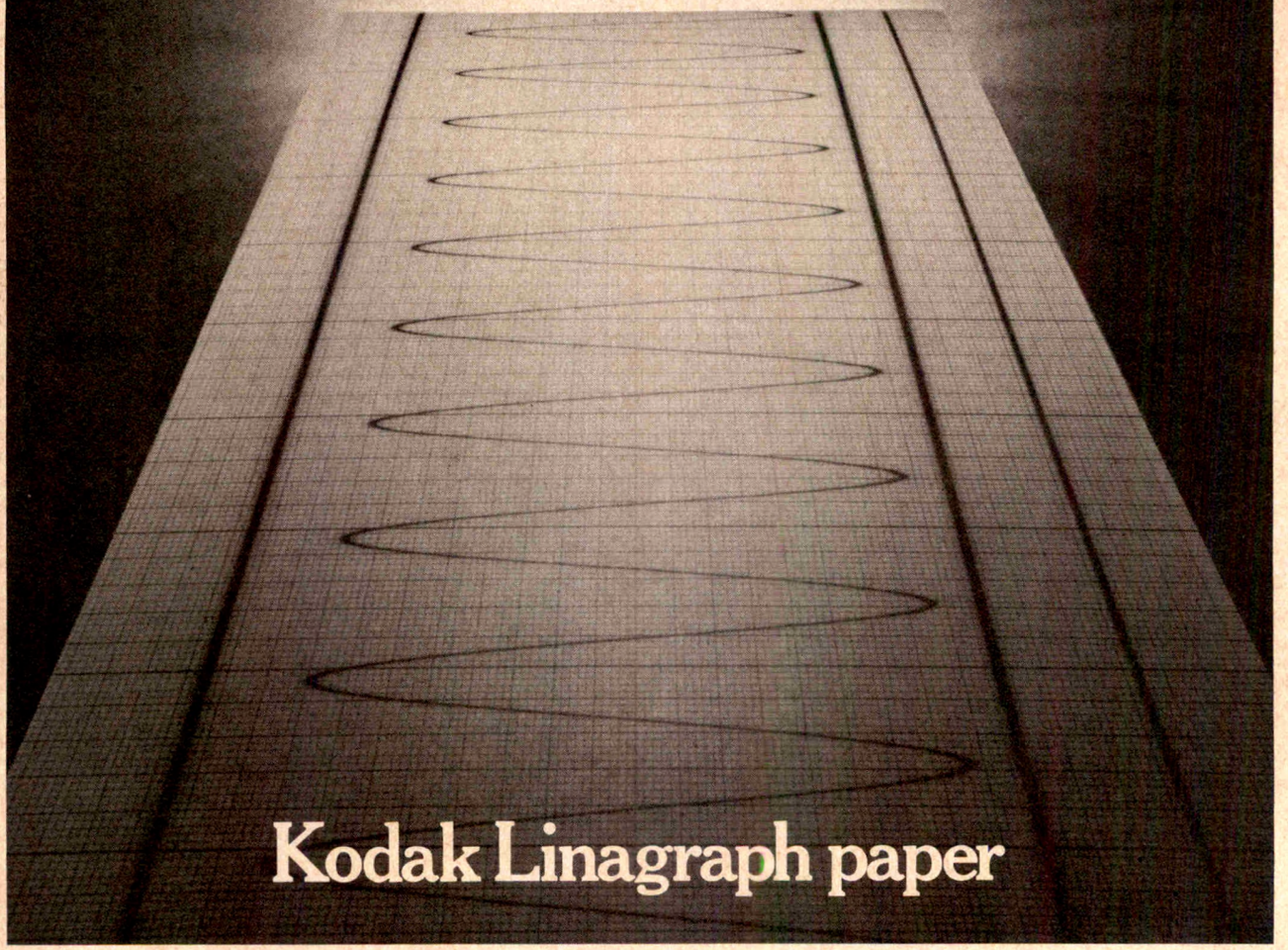

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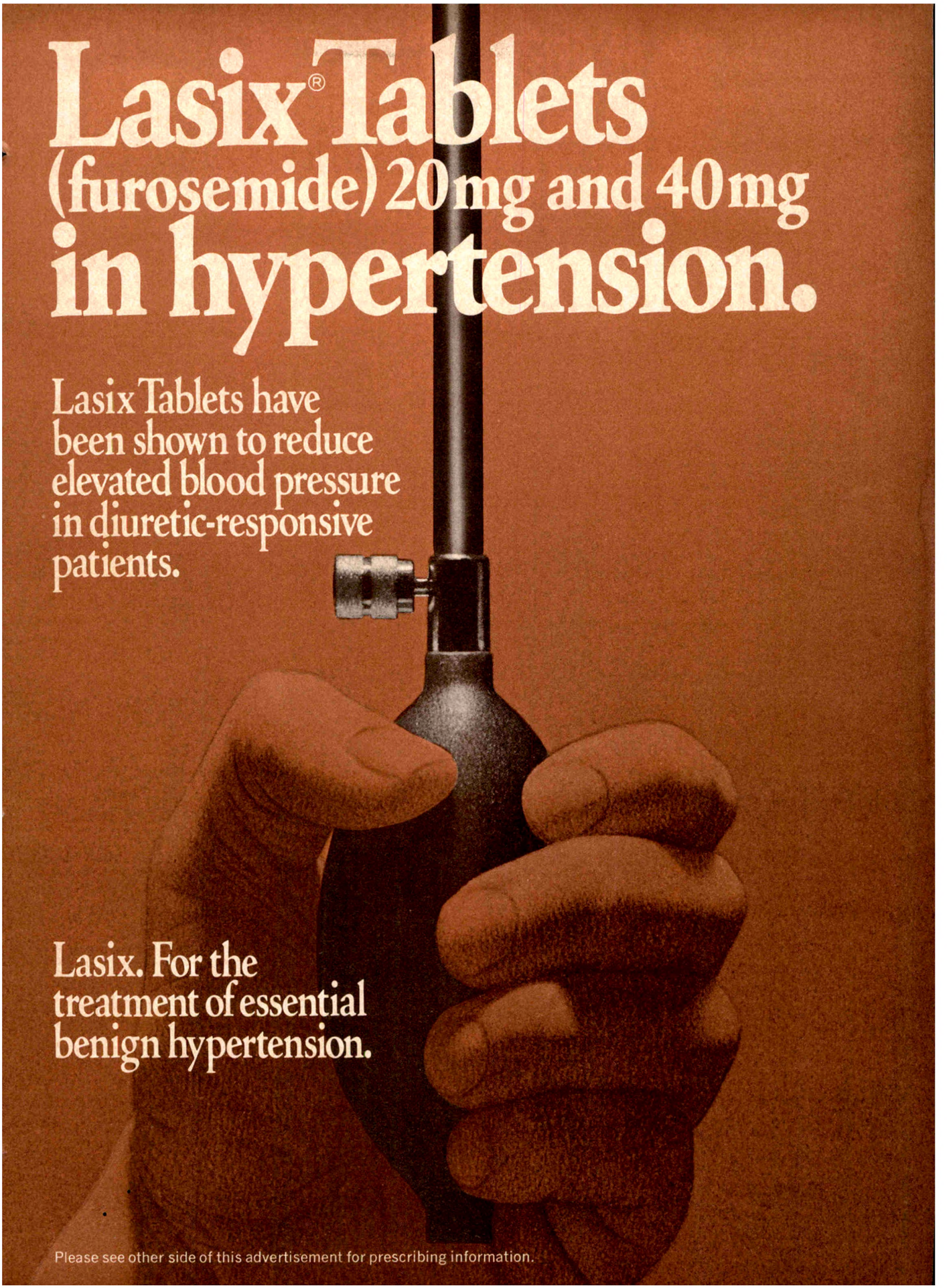
Lasix Tablets have been shown to reduce elevated blood pressure in diuretic-responsive patients.



Lasix. For the treatment of essential benign hypertension.

Please see other side of this advertisement for prescribing information.

Lasix® Tablets (furosemide) 20 mg and 40 mg in hypertension.

A brief summary of the Prescribing Information for

Lasix® (furosemide) Tablets 20 mg and 40 mg

WARNING—Lasix (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Indications—Lasix (furosemide) is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.

Hypertension—Lasix (furosemide) may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix (furosemide) alone.

CONTRAINDICATIONS—Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. (See "Additional Information.")

Lasix (furosemide) is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with a history of hypersensitivity to this compound.

Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

Patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, an oral liquid preparation should be used rather than enteric-coated potassium salts.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix (furosemide).

Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

When parenteral use of Lasix (furosemide) precedes its oral use, it should be kept in mind that cases of tinnitus and reversible hearing impairment have been reported. There have also been some reports of cases in which irreversible hearing impairment occurred. Usually, ototoxicity has been reported when Lasix (furosemide) was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were often given. If the physician elects to use high dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable (for adults, it has been reported that an infusion rate not exceeding 4 mg Lasix [furosemide] per minute has been used).

Increases in blood glucose, and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix (furosemide) may lower serum calcium levels, and rare cases of tetany have been reported.

Patients receiving high doses of salicylates, in conjunction with Lasix (furosemide) may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, Lasix (furosemide) and cephaloridine should not be administered simultaneously.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue Lasix (furosemide) for one week prior to any elective surgery.

Adverse Reactions—Various forms of dermatitis, including urticaria and rare forms of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura). Rare cases of agranulocytosis which responded to treatment.

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli and acute pancreatitis.

Lasix (furosemide)-induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

Dosage and Administration

ADULTS

The usual adult dose of Lasix (furosemide) is 20 to 80 mg given as a single dose.

If the diuretic response with a single dose of 20 to 80 mg is not satisfactory, the following schedule should be used: Increase this dose by increments of 20 or 40 mg not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. The dose of Lasix (furosemide) may be carefully titrated up to 600 mg per day in those patients with severe clinical edematous states.

With doses exceeding 80 mg/day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension—The usual dose of Lasix (furosemide) is 40 mg twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50 percent as soon as Lasix (furosemide) is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix (furosemide), a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if 40 mg twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents, e.g., reserpine, rather than to increase the dose of Lasix (furosemide).

INFANTS AND CHILDREN

Pediatric Administration: The usual initial dose of oral Lasix in infants and children is 2 mg/kg body weight, given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg not sooner than 6 to 8 hours after the previous dose. Doses greater than 6 mg/kg body weight are not recommended.

For maintenance therapy in infants and children, the dose should be adjusted to the minimum effective level.

How Supplied—Lasix Tablets 40 mg (furosemide) supplied as white, round, monogrammed, scored tablets.

Lasix Tablets 20 mg (furosemide) supplied as white, oval, monogrammed tablets.

Note: Dispense in dark containers. Exposure to light may cause slight discoloration which, however, does not alter potency.

Additional Information

Toxicology

The acute toxicity of Lasix (furosemide) has been determined in mice, rats, and dogs. In all three animal species, the oral LD_{50} of Lasix (furosemide) exceeded 1000 mg/kg of body weight, while the intravenous LD_{50} ranged from 300 to 680 mg/kg. Intragastric injection of the drug in newborn rats resulted in an LD_{50} of 380 mg/kg.

The acute toxicity of high doses of Lasix (furosemide) was characterized by convulsions, paralysis, and collapse. Surviving animals often became dehydrated and depleted of electrolytes due to the diuresis induced by Lasix (furosemide). In the newborn rats, intragastric injection of the drug caused hyperactivity and anorexia.

Chronic toxicity studies with Lasix (furosemide) were done in rats and dogs. In a one-year study in rats, renal tubular degeneration occurred, with all doses higher than 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day). A six-month study in dogs revealed calcification and scarring of the renal parenchyma at all doses above 10 mg/kg (83 percent of the maximal recommended human dose of 600 mg per day).

Reproductive Studies

The effects of Lasix (furosemide) on embryonic and fetal development and on pregnant dams were studied in mice, rats, and rabbits.

Lasix (furosemide) caused unexplained maternal deaths and abortions in the rabbit when 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day) was administered between days 12 to 17 of gestation. In a previous study the lowest dose of only 25 mg/kg (2 times the maximal recommended human dose of 600 mg per day) caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality which can precede maternal deaths.

The results of the mouse study and one of the three rabbit studies also showed an increased incidence of hydronephrosis (distention of the renal pelvis and, in some cases, of the ureters) in fetuses derived from treated dams as compared to the incidence in fetuses from the control group.

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Each tablet contains:
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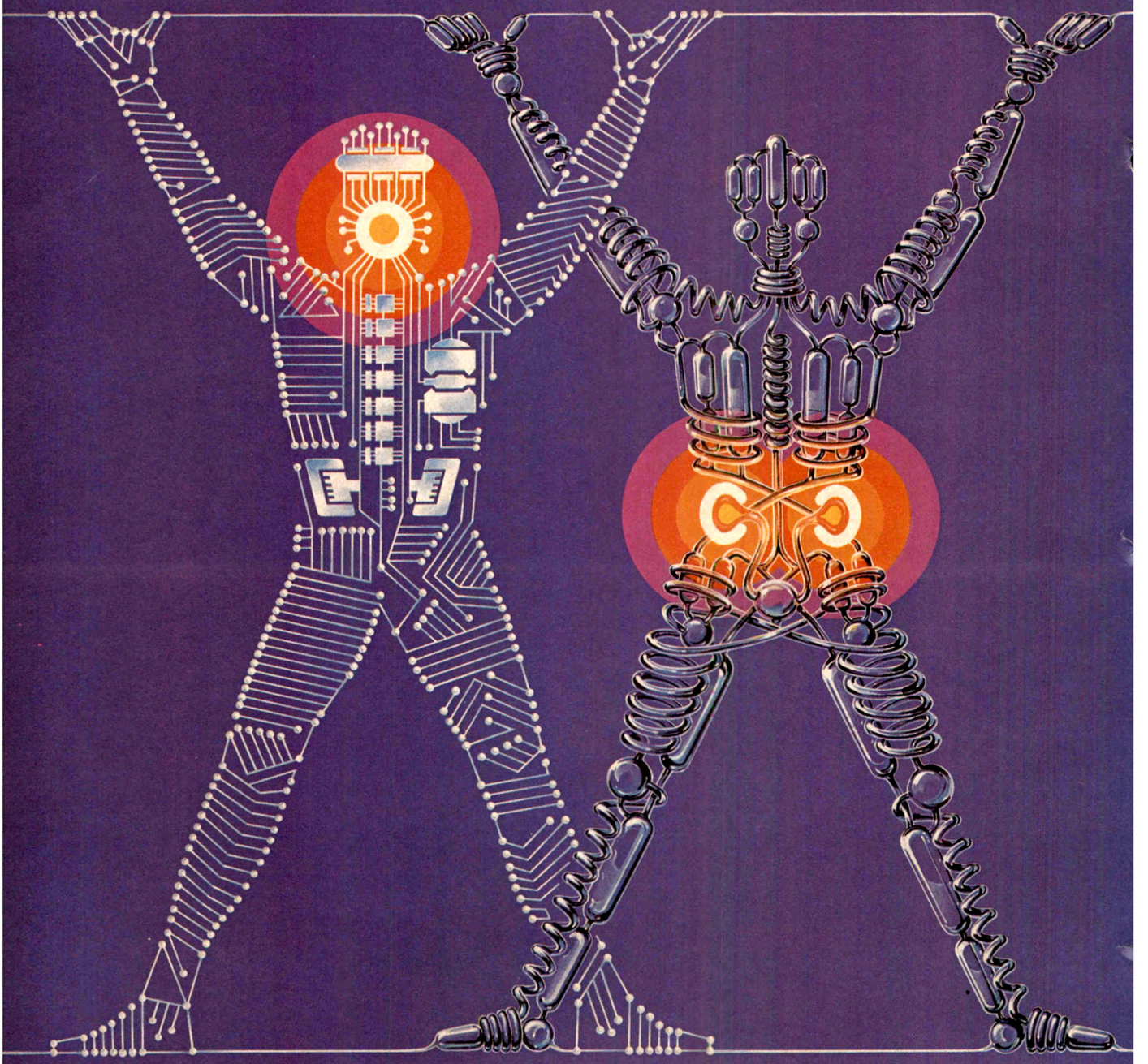
0.1 or 0.2 mg and chlorthalidone, 15 mg

.1 and .2

The only major new combination antihypertensive in a decade



Please see brief summary of the prescribing information including precautions, warnings, adverse reactions.

nonreserpine

Combipres® 1 and 2

Each tablet contains:
Catapres® brand of clonidine hydrochloride, 0.1 or 0.2 mg and chlorthalidone, 15 mg

Works better than either component in equivalent doses*

Works in mild to severe hypertension

Works conveniently for patients who need more than one drug*

Works for less than the cost of separate Rxs*

Works and works and works—convenience and economy promote long-term patient compliance

*Combipres is not indicated for initial therapy of hypertension. It is indicated for hypertensive patients who need more than one drug for adequate lowering of blood pressure and who have proved to be responsive to its components given separately in dosages equivalent to those in the combination.

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

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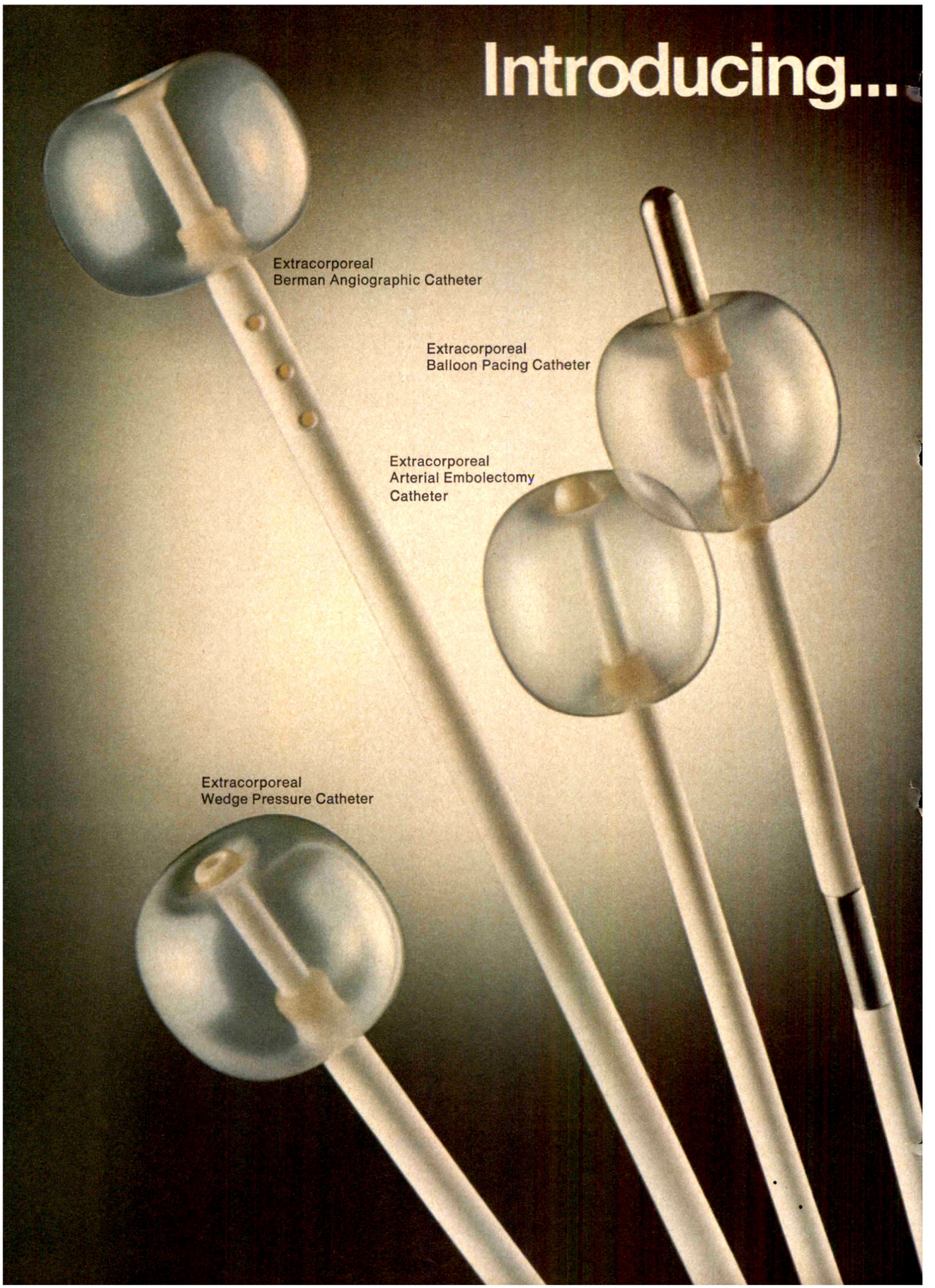
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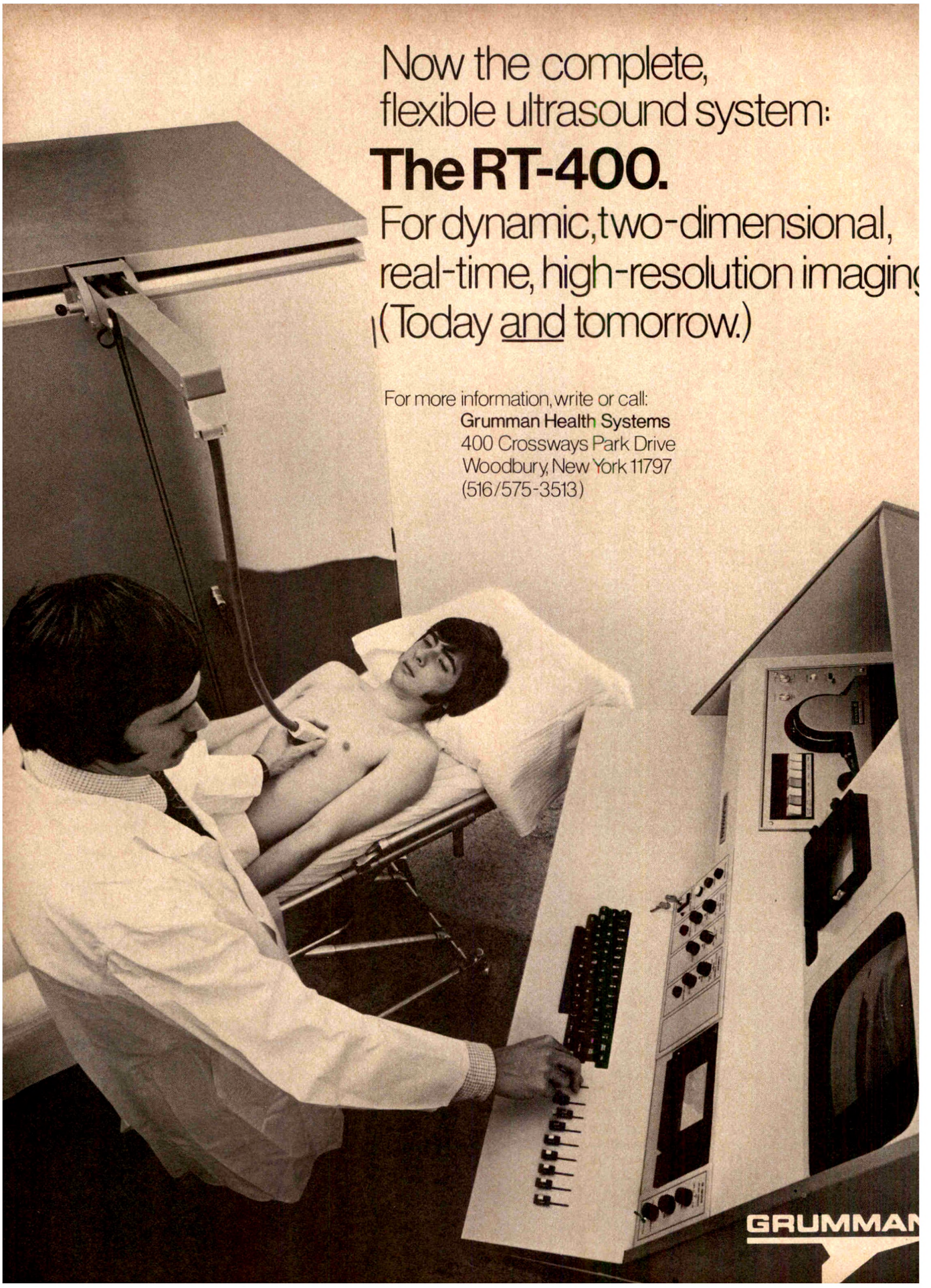
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Arlidin® 6 mg.
(nylidrin HCl)
Vasodilator/Vasorelaxant

- ☐ Dilates arterioles
- ☐ Maintains mean arterial blood pressure
- ☐ Postural hypotension not reported**

Arlidin also offers dosage flexibility and provides a favorable benefit-cost ratio.

Start with Arlidin 6 mg. t.i.d.

**See Adverse Reactions section in Brief Summary.

Brief Summary

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).

USV PHARMACEUTICALS

USV PHARMACEUTICAL MFG. CORP.
Manati, P.R. 00701

In Refractory Congestive Failure Associated with Hypotension or Shock

INTROPIN®
(dopamine HCl)

Provides Patients with a Third Dimension of Therapy

Intropin: a logical addition for hospitalized patients refractory to digitalis and diuretics

When cardiac output is insufficient, or when renal blood flow and urine output do not respond in spite of therapy, a new dimension should be considered as an adjunct to the standard digitalis/diuretic regimen.

Intropin (at recommended doses) may potentiate digitalis/diuretic therapy in two ways. First, Intropin exerts a positive inotropic effect which can result in greater cardiac output, increased renal blood flow and diuresis. In addition, Intropin directly stimulates "dopaminergic" receptors in the kidney to cause renal dilation, increased urine flow and sodium excretion.

Thus, Intropin works both indirectly and directly on the renal vascular beds to decrease accumulated fluids.

Pharmacologic guidelines for adding Intropin to the treatment of patients refractory to digitalis/diuretic therapy

	Cardiac Output	Renal Blood Flow	Urine Flow	Sodium Excretion
DIGITALIS	no change to increase ↑	increase only if cardiac output increases (no direct effect) ↑	increase only if renal blood flow increases ↑	increase only if renal blood flow increases ↑
DIURETICS	no effect	no effect	increase due to increased sodium excretion ↑	increase (direct effect) ↑
INTROPIN®	increase above 5 mcg/kg/min ↑	increase 2-30 mcg/kg/min ↑	increase 2-30 mcg/kg/min ↑	increase if renal blood flow increases 2-30 mcg/kg/min ↑

This chart graphically demonstrates:

1. the effects of digitalis on renal blood flow, urine output and sodium excretion are primarily related to cardiac output;
2. diuretics, while favorably affecting urine flow and sodium excretion, do not influence cardiac output or renal blood flow;
3. Intropin favorably affects cardiac output at doses above 5 mcg/kg/min and increases renal blood flow, urine output and sodium excretion at doses of 2 to 30 mcg/kg/min, regardless of the effect of the drug on cardiac output.

Intropin: a catecholamine with unique actions

Intropin is a unique catecholamine that increases cardiac output, vital organ perfusion and urine output without increasing the likelihood of serious side effects. With Intropin, the myocardial oxygen supply/demand ratio appears to remain stable.

Concurrent administration of Intropin and diuretic agents may produce an additive or potentiating effect.

As with most drugs administered in serious situations, a key to favorable prognosis is the initiation of Intropin as soon as practical after the onset of unfavorable signs. Patients most likely to respond are those whose myocardial function, urine output and blood pressure have not undergone profound deterioration.

Intropin: points about dosage

Before administering Intropin, the physician should be familiar with the effects of the drug at various dosage levels (see chart) and should especially note the paradoxical results of Intropin at ranges of over 30 mcg/kg/min—increases in systemic vascular resistance plus a decrease in renal blood flow and urine output. These norepinephrine-like phenomena can be reversed, if desired, by reducing the dose.

Intropin is compatible with digitalis and diuretics employed in the treatment of refractory congestive heart failure.

Intropin must be diluted in a suitable intravenous solution and given by I.V. drip under close medical supervision.

The half-life of Intropin is somewhat less than 2 minutes, and all effects of the drug usually dissipate within 10 minutes after cessation of the medication.

The effects of Intropin at various dose levels

	2-5 mcg/kg/min	5-30 mcg/kg/min	over 30 mcg/kg/min
Cardiac Output	no change	increase	increase
Stroke Volume	no change	increase	increase
Heart Rate	no change	there is an initial increase followed by a decrease toward normal rate as infusion continues	
Myocardial Contractility	no change	increase	increase
Potential for Excessive Myocardial Oxygen Demands	low* coronary blood flow increased	low* coronary blood flow increased	data unavailable
Potential for Tachyarrhythmias	low*	low*	moderate
Total Systemic Vascular Resistance	slight decrease to no change	no change to slight increase	increase
Renal Blood Flow	increase	increase	decrease
Urine Output	increase	increase	decrease

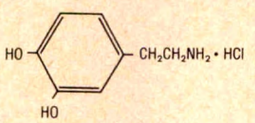
*Low but needs monitoring

See the following page for full prescribing information.

INTROPIN®
(dopamine HCl)

INTROPIN® (dopamine HCl)
5 ml. AMPUL/FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs — Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output — Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension — Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy — Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children — The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia — Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure — If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation — INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease — Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT — Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics — Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required — Close monitoring of the following indices — urine flow, cardiac output and blood pressure — during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution — Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration — INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Adminstration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter. September, 1975

ARNAR-STONE LABORATORIES, INC.
Mount Prospect, Illinois 60056
A Subsidiary of American Hospital Supply Corporation

Printed in U.S.A.

ASL-09-76-934

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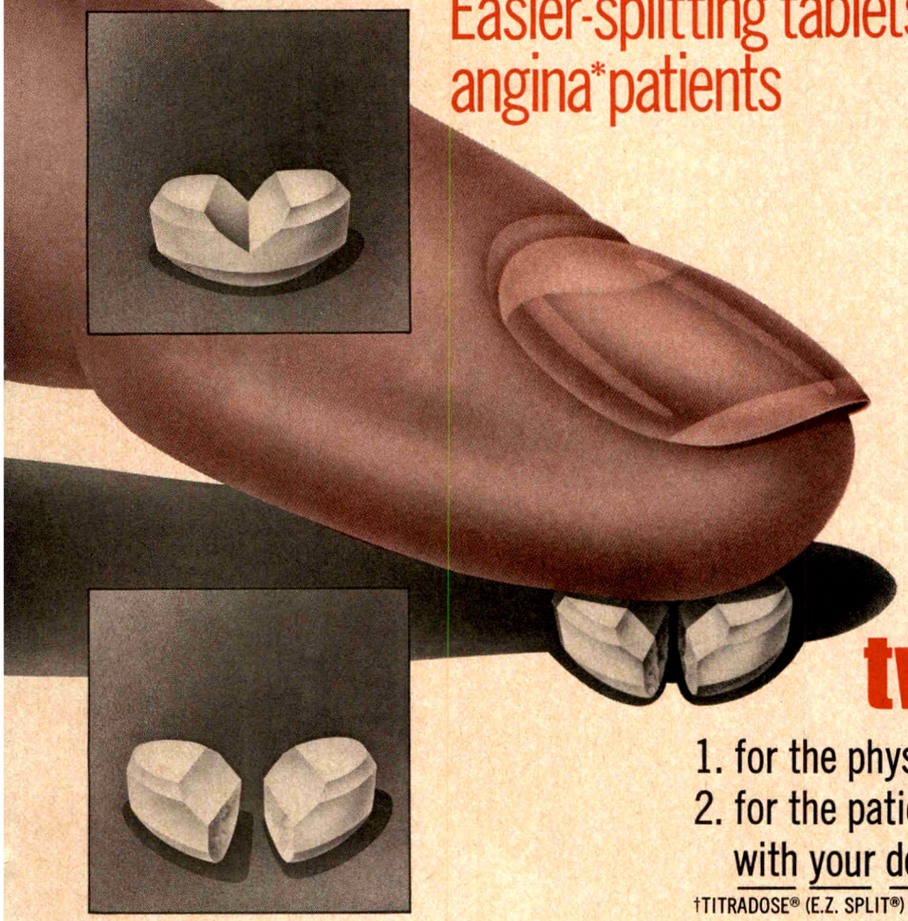

One press of a finger solves two problems

1. for the physician: precise dosage titration
2. for the patient: easier compliance with your dosage adjustments

†TITRADOSE® (E.Z. SPLIT®) Oral Tablets, U.S. Pat. Nos. D224591 and 3883647

ISORDIL® TITRADOSE® ORAL TABLETS
(isosorbide dinitrate)

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

May we send you reprints, detailed information and/or professional samples?

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New York, New York 10017

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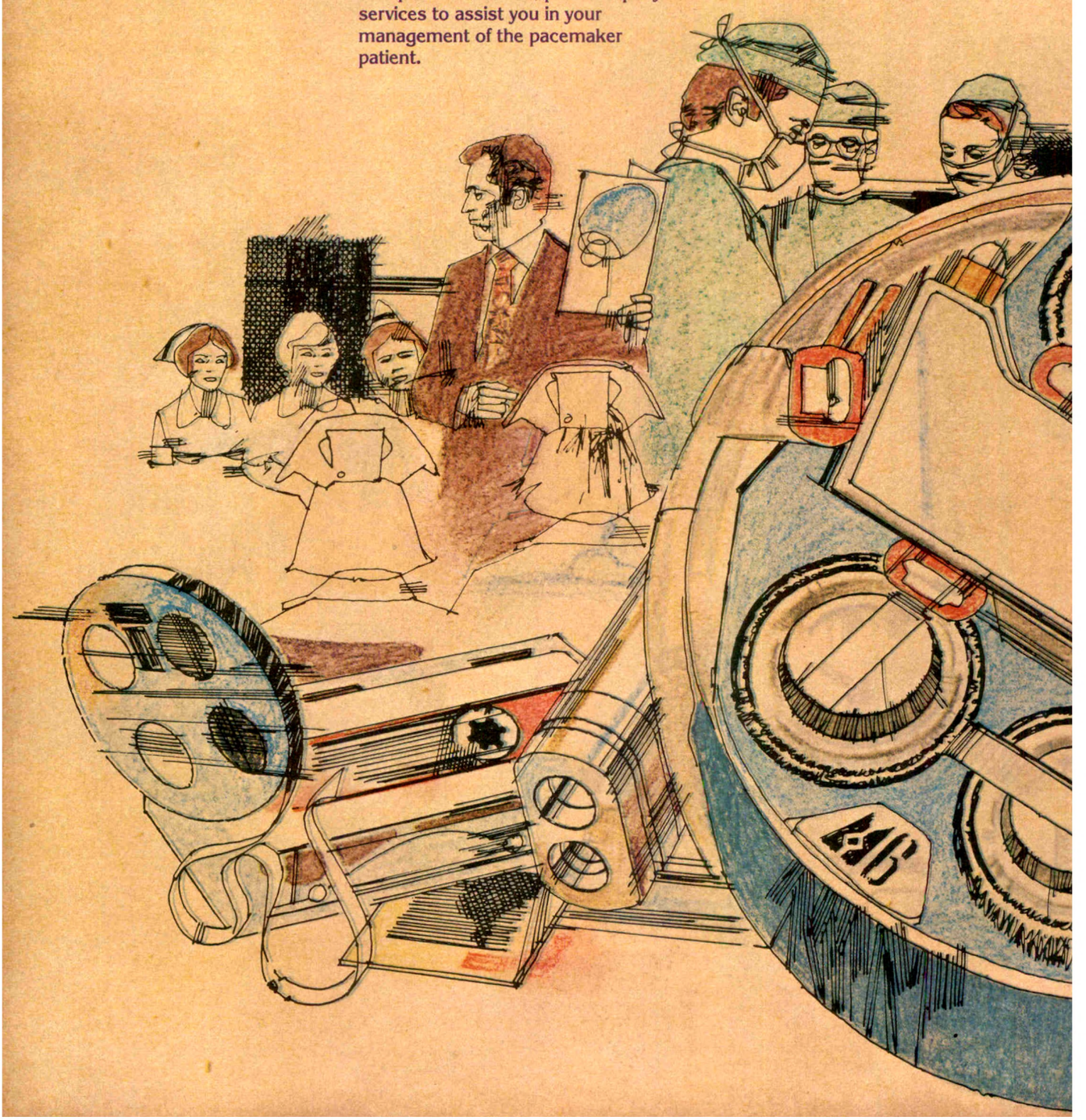

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QUALITY AND RELIABILITY As you probably are aware, quality and reliability are particularly emphasized at Medtronic. One of every five persons involved with the manufacture of our products is assigned quality or reliability control responsibilities to assure that our products will meet or exceed industry standards.

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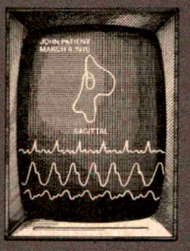

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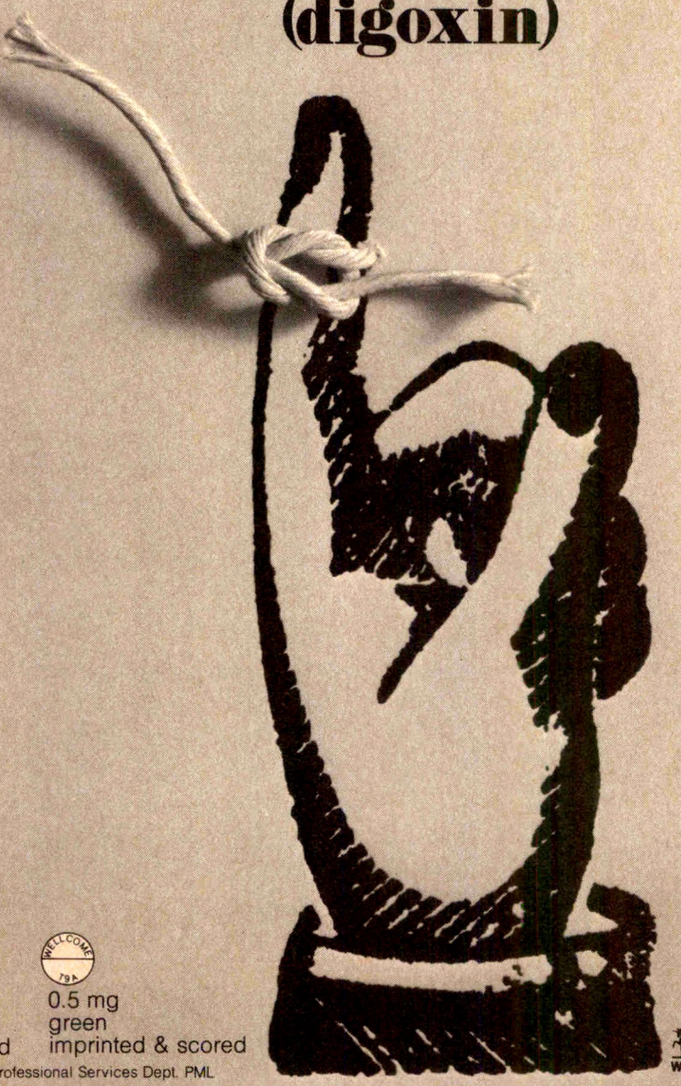

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CLINICAL STUDIES

Prosthetic Valve Endocarditis

Clinicopathologic Analysis of 22 Necropsy Patients With Comparison of Observations in 74 Necropsy Patients With Active Infective Endocarditis Involving Natural Left-Sided Cardiac Valves

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Clinical and morphologic features are described in 22 necropsy patients with endocarditis involving rigid-framed prosthetic valves: aortic in 15 patients and mitral in 7. The interval from valve replacement to onset of symptoms of prosthetic valve endocarditis was less than 2 months in 8 patients and longer than 2 months in 14 patients. The most frequent infecting organism was the Staphylococcus (13 patients). In each of the 22 patients the infection was located behind the site of attachment of the prosthesis to the valve ring, and the infection spread to adjacent structures in 13 patients, 11 of whom had aortic prostheses. Prosthetic detachment causing severe regurgitation occurred in 12 ot the 15 patients with an infected aortic valve prosthesis, and in 2 of the 7 with an infected mitral valve prosthesis. Prosthetic obstruction by vegetative material occurred in 5 of 7 patients with prosthetic mitral infection and in only 1 of 15 with prosthetic aortic infection. High degrees of conduction defects developed in seven patients with aortic prosthetic valve endocarditis: complete heart block in five, and complete left bundle branch block in two.

Comparison of observations in the 22 patients with prosthetic valve endocarditis with those in 74 patients with active infective endocarditis involving natural left-sided cardiac valves revealed significant ($P < 0.05$) differences in the percent with ring abscess, hemodynamic consequences of the endocarditis (valve stenosis), frequency of Staphylococcus as the causative organism and percent with complete heart block or left bundle branch block. No significant differences were observed between the two groups when comparing age, sex, type of underlying valve disease or frequency of organ infarcts or splenomegaly.

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Among 450 consecutive patients with one or more rigid-framed prosthetic cardiac valves studied by us at necropsy,[1–7] 22 (5 percent) had infection involving a prosthetic valve. These 22 patients represent 17 percent of the 127 patients with active valvular infective endocarditis studied in this laboratory.[8–10] Although many reports are available on patients with fatal active infective endocarditis involving natural cardiac valves, surprisingly little information is available on the morphologic

features of endocarditis involving prosthetic cardiac valves. This report consequently focuses on the clinicopathologic features in 22 patients with prosthetic valve endocarditis and compares them with the features we observed in 74 nonsurgical necropsy patients with active infective endocarditis involving natural left-sided cardiac valves.

Patients Studied

Clinical observations: Clinical and morphologic observations in the 22 patients with prosthetic valve

TABLE I

Prosthetic Valve Endocarditis: Type of Prosthesis Infected

	Aortic Valve	Mitral Valve	Totals
Caged ball	9*	6*	15*
Tilting disc	5†	0	5†
Poppet disc	1‡	1§	2
Totals	15	7	22

* Starr-Edwards; † Björk-Shiley; ‡ Hufnagel; § Kay-Shiley.

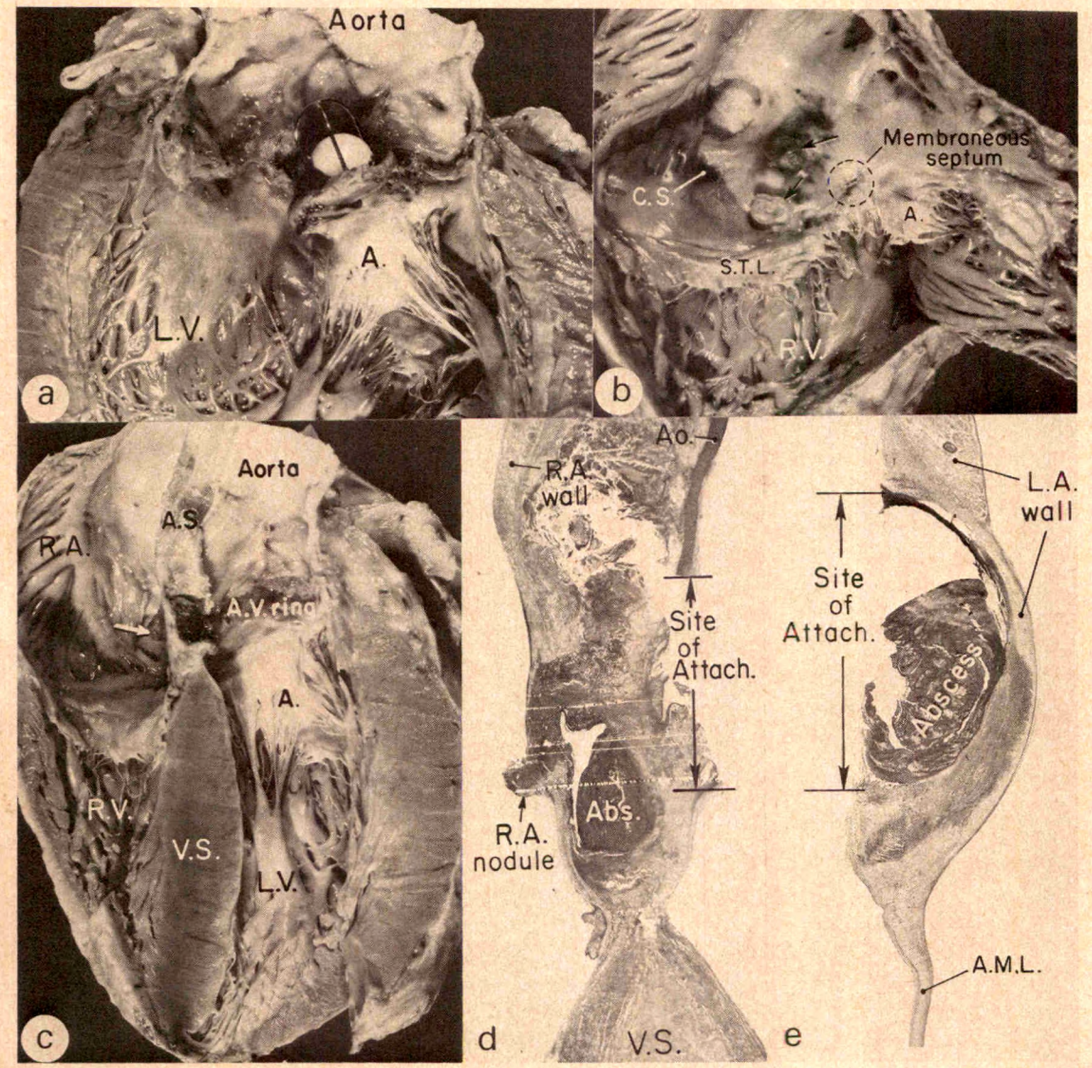

FIGURE 1. Staphylococcus epidermidis prosthetic valve endocarditis in a 49 year old man who died 3 months after aortic valve replacement. Symptoms of infection appeared 16 days before death. Despite large doses of antibiotic agents, complete heart block and severe aortic regurgitation developed. **a,** opened aorta, aortic valve and left ventricle (L.V.) showing a necrotic anulus to which the prosthesis is only partially attached. A. = anterior mitral leaflet. **b,** opened right atrium, tricuspid valve and right ventricle (R.V.) showing vegetative material **(arrows)** that had burrowed through the atrial septum from the necrotic aortic valve ring. C.S. = ostium of coronary sinus; S.T.L. = septal tricuspid leaflet; A. = anterior tricuspid leaflet. **c,** longitudinal section of the heart with the anterior portion removed. The necrotic aortic valve (A.V.) ring is again seen and the penetration of the infective process through the atrial septum (A.S.) is apparent. An **arrow** indicates the vegetation in the right atrium (R.A.). V.S. = ventricular septum. **d** and **e,** histologic sections through the ring abscess. The site of attachment (Attach.) of the prosthesis, which has been removed, is indicated. The infected nodule, an extension of the ring abscess (Abs.), is showing in the right atrium. Ao. = aortic wall; L.A. = left atrium; A.M.L. = anterior mitral leaflet.

TABLE II

Prosthetic Endocarditis: Clinical Observations in 22 Cases

Prosthesis Infected	Patients no.	Patients Age Range and Average (yr)	Patients Sex M	Patients Sex F	Preop Lesion Steno-sis	Preop Lesion Pure Re-gurgi-tation	Interval From Valve Replacement to Infection <2 mo	Interval From Valve Replacement to Infection >2 mo	Duration of Signs and Symptoms of Infection <60 Days	Duration of Signs and Symptoms of Infection >60 Days	Patients Receiving Anti-biotics >7 Days (no.)	Conduction Disturbance LBBB	Conduction Disturbance CHB	Prosthetic Dysfunction Re-gurgi-tation	Prosthetic Dysfunction Steno-sis
Aortic	15	37–69 (54)	13	2	12	3	5	10	10	5	9	2	5	11	1
Mitral	7	37–65 (52)	3	4	7	0	3	4	6	1	2	0	0	0	0
Totals	22	37–69 (53)	16	6	19	3	8	14	16	6	13	2	5	11	1

CHB = complete heart block; LBBB = left bundle branch block; Preop = preoperative.

endocarditis are summarized in Tables I to V, and some of the morphologic features are illustrated in Figures 1 to 11. Certain observations in several of these patients have appeared elsewhere.[1–3,11–13] Patients with active infective endocarditis at the time of valve replacement were excluded. The 22 patients had 27 prosthetic cardiac valves; 17 patients had one prosthetic valve and 5 had two prosthetic valves. Of the 27 prosthetic valves, 22 were infected (Table I): the aortic prosthesis in 15 patients and the mitral in 7. Clinical evidence of infective endocarditis was present less than 2 months after operation in 8 patients (early deaths) (Table II), and from 3 months to 10 years after valve replacement in 14 patients. In 6 of the latter 14 patients clinical evidence of infection did not appear until more than 1 year after valve replacement. The duration of signs and symptoms of infective endocarditis ranged from 14 days to 13 months. In 16 patients, the duration of illness was less than 60 days and, in 6 patients, more than 60 days. Factors predisposing to development of endocarditis were apparent in only 5 of the 14 patients who died late: tooth extraction (2 patients), skin graft infection (1 patient), prolonged use of an intravenous catheter (1 patient) and prolonged use of a transthoracic pacing wire (1 patient). It is presumed that the infection in the eight patients who died early either was incurred at operation or was secondary to a wound infection.

The infecting organisms (cultured from the blood during life in 20 patients) are listed in Table III. Staphylococcus was the responsible organism in 13 patients, and a different organism in each of the other 9. Fungi caused the endocarditis in two patients who had negative blood cultures during life. Evidence of prosthetic dysfunction was present clinically in 12 of the 15 patients with an infected aortic valve prosthesis

TABLE III

Prosthetic Valve Endocarditis: Infecting Organism

Organism	Onset From Valve Replacement <2 mo	Onset From Valve Replacement >2 mo	Totals
I. Gram-positive bacterium	6	11	17
Staphylococcus epidermidis	3	7	10
Staphylococcus aureus	2	1	3
Streptococcus pneumoniae	0	1	1
Group-D streptococcus	0	1	1
Diphtheroids	1	0	1
Listeria monocytogenes	0	1	1
II. Gram-negative bacterium	1	2	3
Proteus mirabilis	1	0	1
Klebsiella species	0	1	1
Serratia marcescens	0	1	1
III. Fungus	1	1	2
Candida species	0	1	1
Aspergillus fumigatus	1	0	1
Totals	8	14	22

TABLE IV

Prosthetic Valve Endocarditis: Necropsy Observations in 22 Cases

Prosthesis Infected	Patients (no.)	Ring Abscess	Ring Organisms	Prosthetic Valve Detach-ment (Re-gurgi-tation)	Pros-thetic Valve Stenosis
Aortic	15	15	8	12	1
Mitral	7	7	5	2	5
Totals	22	22	13	14	6

TABLE V

Prosthetic Valve Endocarditis: Organ Weights and Infarcts in 22 Cases

Prosthesis Infected	Pa-tients (no.)	Organ Weight (g) (range and average) Spleen	Organ Weight (g) (range and average) Liver	Gross Infarcts (no. of patients) Spleen	Gross Infarcts (no. of patients) Kid-ney	Gross Infarcts (no. of patients) Brain
Aortic	15	120–1000 (470)	1450–2950 (2140)	7	3	3
Mitral	7	170–920 (370)	1350–2000 (1755)	5	4	4
Totals	22	120–1000 (460)	1350–2950 (2050)	12	7	7

(regurgitation in 11 and stenosis plus regurgitation in 1), but in none of the 7 patients with an infected mitral valve prosthesis. High grade conduction disturbances occurred in 7 patients, all in the group of 15 with an infected aortic prosthesis: left bundle branch block in 2 and complete heart block in 5. Thirteen of the 22 patients received appropriate antibiotic therapy for more than 7 days. Three patients underwent valve replacement for prosthetic endocarditis. The principal causes of death in the 22 patients were congestive heart failure (19 patients), central nervous system embolus (2 patients) and generalized infection (1 patient).

Morphologic observations: Among the 22 patients, 17 had one valve prosthesis and 5 had two valve prostheses. In each of the five latter patients, only the "downstream" prosthesis was infected: the aortic prosthesis in the three patients with mitral and aortic prostheses, and the mitral prosthesis in the two patients with tricuspid and mitral prostheses. Twelve of the 15 infected aortic valve prostheses and 2 of the 7 infected mitral valve prostheses were partially or completely detached. In contrast, 5 of the 7 infected mitral prostheses and only 1 of the 15 infected aortic prostheses were obstructed by vegetative material.

Ring abscesses (Table IV) were present in each of the 22 infected prostheses; in one the abscess was visible only by histologic examination. The ring abscess involved the entire valve anulus in 14 patients and only portions of the anulus in the other 8. In 13 of the 22 patients the infective process spread to adjacent

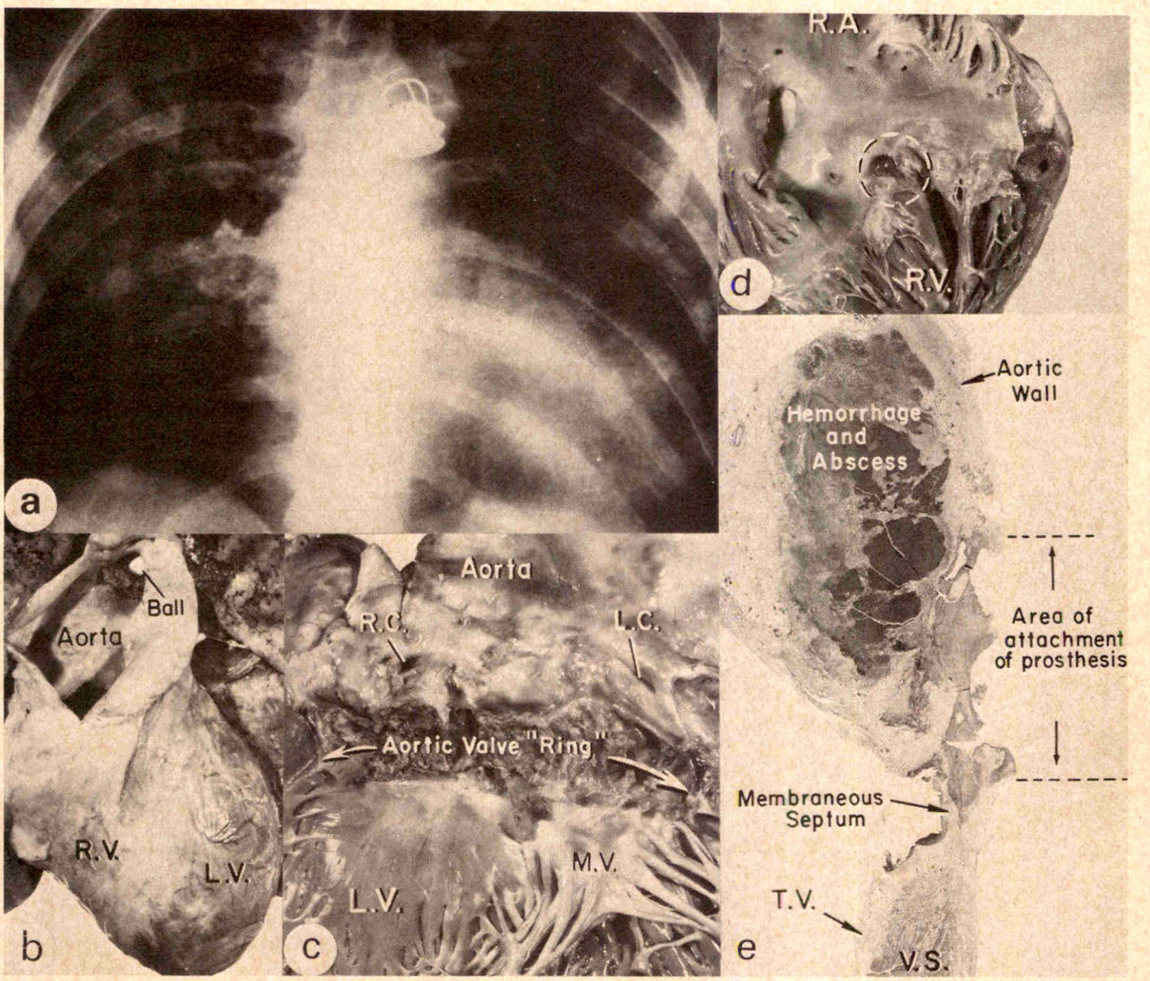

FIGURE 2. Staphylococcus epidermidis prosthetic aortic valve endocarditis in a 48 year old man. He had been well for 11 months after insertion of the Starr-Edwards prosthesis when, 1 month before death and 6 weeks after dental extraction, shaking chills appeared and blood cultures were positive for Staphylococcus epidermidis. Despite intensive antibiotic therapy, signs of aortic regurgitation appeared, and minutes before death he complained of "feeling funny." **a,** chest roentgenogram immediately after death revealed that the prosthesis had dislodged and migrated to the aortic arch. **b,** anterior view of the heart and opened ascending aorta. The detached prosthesis ball is visible, lodged in the transverse aorta. L.V. = left ventricle; R.V. = right ventricle. **c,** opened aorta, aortic valve "ring" and left ventricle showing a totally necrotic aortic anulus. L.C. = ostium of left coronary artery; M.V. = anterior mitral leaflet; R.C. = ostium of right coronary artery. **d,** opened right atrium (R.A.), tricuspid valve and right ventricle showing a ring abscess **(dashed circle)** that had extended from the prosthetic aortic valve anulus. **e,** photomicrograph through the aortic valve "ring" showing a large ring abscess and the necrotic aortic anulus material that extended through the membranous ventricular septum into the right atrium. T.V. = tricuspid valve leaflet; V.S. = ventricular septum. (Hematoxylin-eosin ×2, reduced by 24 percent.)

structures. In 11 of the 15 patients with an infected aortic aortic valve prosthesis the ring abscess burrowed into adjacent structures: through the ascending aorta into the periaortic space (7 patients); through the atrial septum into the right atrium (9 patients) or into the left atrium (2 patients); through the ventricular septum into the right ventricle (8 patients); and into the anterobasal left ventricular wall (2 patients). In two patients with an infected mitral valve prosthesis the ring abscess burrowed through the atrial wall into the pericardial space. Histologic examination of the infected rings disclosed colonies of organisms in 13 of the 22 patients.

Both arterial emboli and gross organ infarcts were common with both prosthetic aortic and prosthetic mitral valve endocarditis (Table V). Grossly visible infarcts were present in the spleen in 12, the kidney in 7 and the brain in 7 of the 22 patients. Two patients had a bowel infarct, one a pancreatic infarct and one a transmural myocardial infarct. In addition, mycotic aneurysms were present in the ascending aorta of three patients: in two patients, aneurysms resulted from jet lesions from the infected prosthesis and, in the third, the cage of the partially detached prosthesis burrowed into the wall of a weakened aorta (after an aortotomy performed weeks earlier) causing a sacular aneurysm.

The spleen ranged in weight from 120 to 1,000 g (average 460) and in 14 of the 22 patients it weighed more than 300 g. The liver ranged in weight from 1,350 to 2,950 g (average 2,050).

Comments

Clinical Features

Incidence: Study of our 22 necropsy patients and analysis of more than 150 necropsy cases of prosthetic valve endocarditis reported by others[14–47] allows certain general conclusions regarding this condition. It is a devastating complication of cardiac valve replacement,

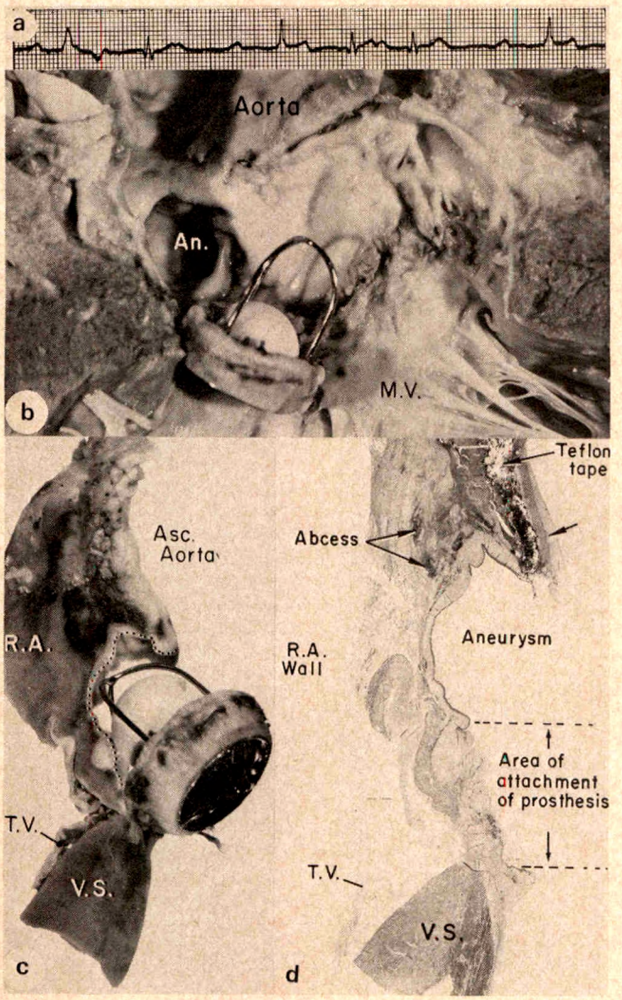

FIGURE 3. Staphylococcus epidermidis prosthetic aortic valve endocarditis in a 55 year old man. The Starr-Edwards prosthesis was used to replace an infected trileaflet Teflon® (Muller) valve 45 days before death. **a,** electrocardiogram revealing complete heart block and signs of massive aortic regurgitation that appeared despite antibiotic therapy. **b,** opened aorta, aortic valve and left ventricle. The aortic valve ring is necrotic, and the prosthesis is almost totally detached. The cage of the prosthesis has burrowed into the wall of the aorta causing a saccular aneurysm (An.). M.V. = mitral valve. **c,** longitudinal section showing the caged ball prosthesis burrowing into the ascending (Asc.) aorta, producing the aneurysm. R.A. = right atrium; T.V. = septal tricuspid valve leaflet; V.S. = ventricular septum. **d,** photomicrograph through the same area after removal of the prosthesis. (Hematoxylin-eosin ×2, reduced by 25 percent.)

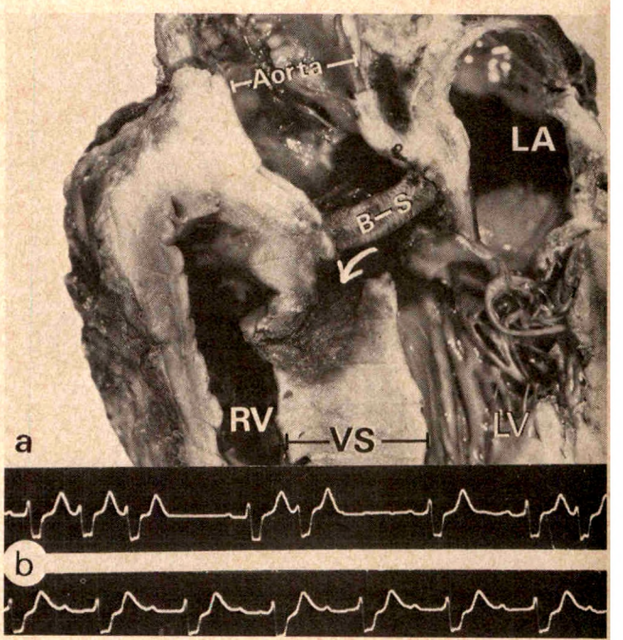

FIGURE 4. Staphylococcus epidermidis prosthetic aortic valve endocarditis in a 51 year old man. The stenotic bicuspid aortic valve had been replaced with a Björk-Shiley prosthesis 83 days before death. Fever was present in the early postoperative period, and shortly before death complete heart block and signs of congestive heart failure appeared. **a,** longitudinal section of the heart with the anterior portion removed. The Björk-Shiley (B-S) prosthesis is partially detached and the ring abscess **(arrow)** has burrowed through the ventricular septum (VS) into the right ventricle (RV). LA = left atrium; LV = left ventricle. **b,** rhythm strip obtained shortly before death revealing complete heart block.

but fortunately it is infrequent. The exact incidence rate is uncertain but it is clearly less than 1 percent annually among patients with prosthetic cardiac valves.[37,39,45,48] Although prospective studies[49,50] have been inconclusive, retrospective studies[16,17,51,52] have shown a reduction in the frequency of early (less than 2 months after valve replacement) endocarditis coincident with the use of prophylactic antibiotic therapy. Late prosthetic valve infection now appears to be more common than early infection,[37,45] presumably because there are now so many persons with prosthetic cardiac valves. Although the mortality rate is high for both groups,

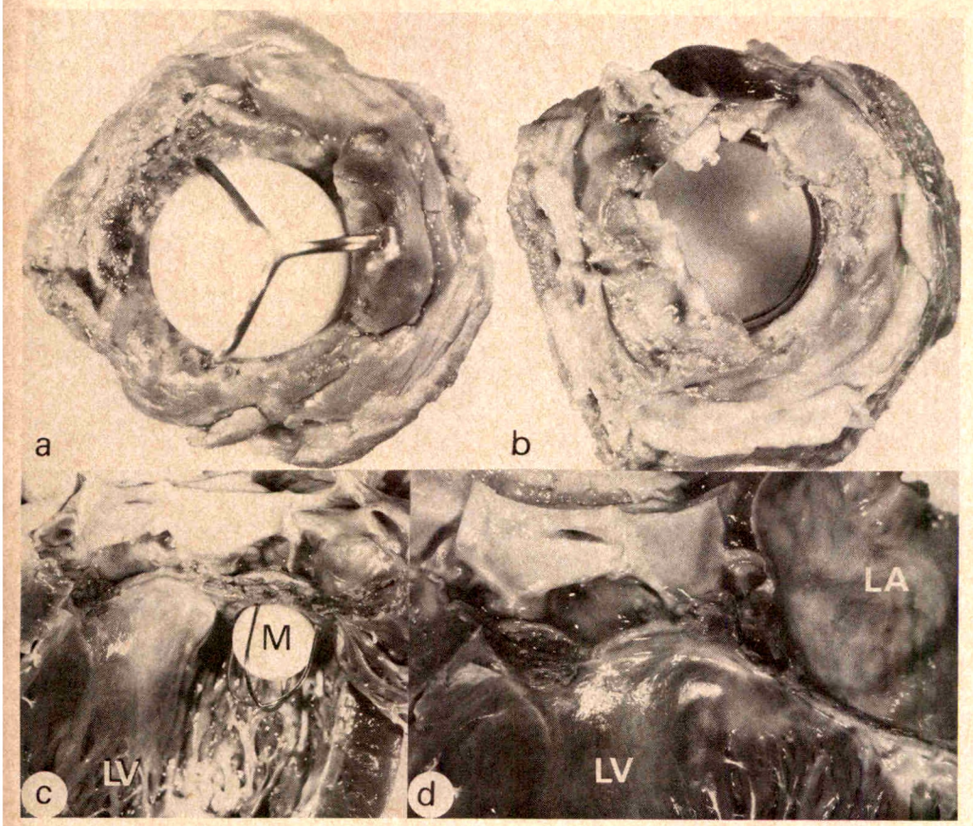

FIGURE 5. Serratia marcescens prosthetic aortic valve endocarditis in a 57 year old man whose infection occurred 4 months after replacement of both aortic and mitral valves. The apparent source of the infection was an intravenous catheter. Left bundle branch block and signs of aortic regurgitation appeared and, despite massive doses of antibiotic agents, he died 3 months after the onset of symptoms of infection. **a,** view of the aortic prosthesis from above. Infected thrombus is present on its anulus. **b,** view of the prosthesis as it appeared from the left ventricle. Some of the infected thrombus became detached during excision of this prosthesis at necropsy. The primary orifice is partially obstructed by the infected material. **c,** opened aortic root, aortic valve and left ventricle (LV) after removal of the aortic prosthesis. Most of the aortic ring is necrotic. In addition, the portion of mitral (M) prosthesis in direct apposition to the aortic anulus also is infected. **d,** view after excision of the mitral prosthesis showing extension of the aortic anular infection into the junctional area between the aortic and mitral anuli. LA = left atrium.

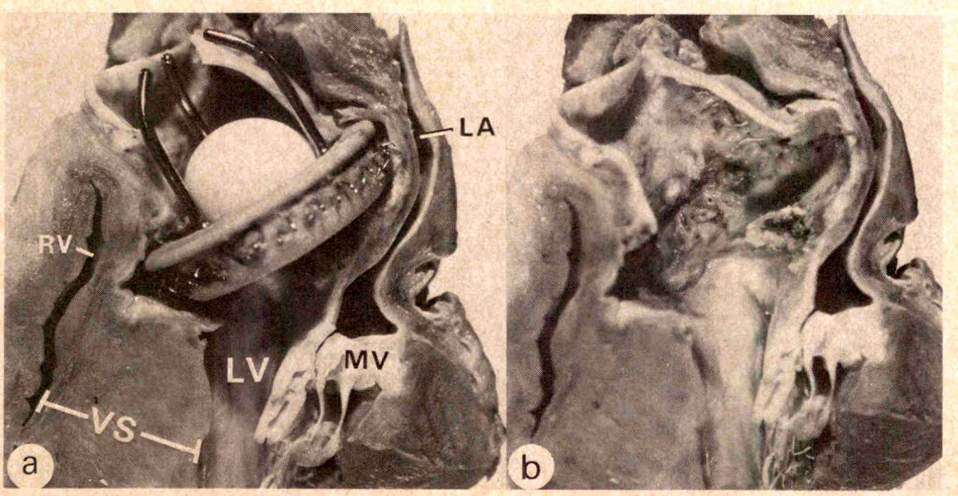

FIGURE 6. Staphylococcus epidermidis endocarditis originally involving a Björk-Shiley aortic valve prosthesis that was excised and replaced with a Magovern prosthesis 28 days before death in a 69 year old man. Fever and signs of aortic regurgitation appeared 7 months after aortic valve replacement with the Björk-Shiley prosthesis. After replacement with the Magovern prosthesis, a murmur of aortic regurgitation reappeared. At necropsy, the sewing ring of the Magovern prosthesis had burrowed deeply into the necrotic anulus, causing the ball of the prosthesis to strike the nonnecrotic portion of the aortic wall, probably producing prosthetic aortic stenosis. **a,** longitudinal section of the heart through the aortic anulus with the Magovern prosthesis in place; **b,** section after removal of the prosthesis. The frame of the prosthesis has burrowed deeply into the necrotic anulus. LA = left atrium; LV = left ventricle; MV = mitral valve; RV = right ventricular cavity; VS = ventricular septum.

early prosthetic valve infection apparently is more often fatal than late infection.[37,39,45,48]

Etiology: Most early infections either are incurred at operation or result from a wound infection.[25,29,37,39,48] Those at operation appear to result from contamination of the cardiopulmonary bypass equipment.[53,54] Staphylococcus is the organism cultured most frequently from cardiopulmonary bypass equipment and it is the most frequent cause of early prosthetic valve endocarditis.[14,16–18,25,30,37,39,44,45] When gram-negative bacteria or fungi cause endocarditis early, they are usually also recovered from the operating room equipment or from a wound infection.[28,39] Late infections usually result from transient bacteremias.[37,39,45,48] Although both staphylococci and streptococci are frequent causes of clinically diagnosed late prosthetic valve endocarditis,[37,39,45] the former have caused most cases of necropsy-proved late endocarditis and the latter relatively few. In none of our 22 necropsy patients was the infection caused by Streptococcus. Staphylococcus was the most common cause of endocarditis in our patients whether the infection occurred early or late.

Blood cultures: Among patients with prosthetic valve endocarditis, blood cultures are almost always positive, except when the infections are caused by certain fungi.[27,28,31,32,37,39,44,45,48] Blood cultures were positive during life in each of our 20 patients with endocarditis caused by bacteria and were negative in each of our 2 patients with fungal endocarditis. Blood cultures were positive in only 3 of 39 patients with endocarditis caused by Aspergillus species in a series reviewed by Kammer and Utz.[55]

Prosthetic valve dysfunction: Signs of prosthetic valve dysfunction are usually present when the aortic prosthesis is infected and usually absent when the mitral prosthesis is infected. Clinical signs of aortic regurgitation were present in 11 of our 15 patients with an infected aortic valve prosthesis. In three of the four

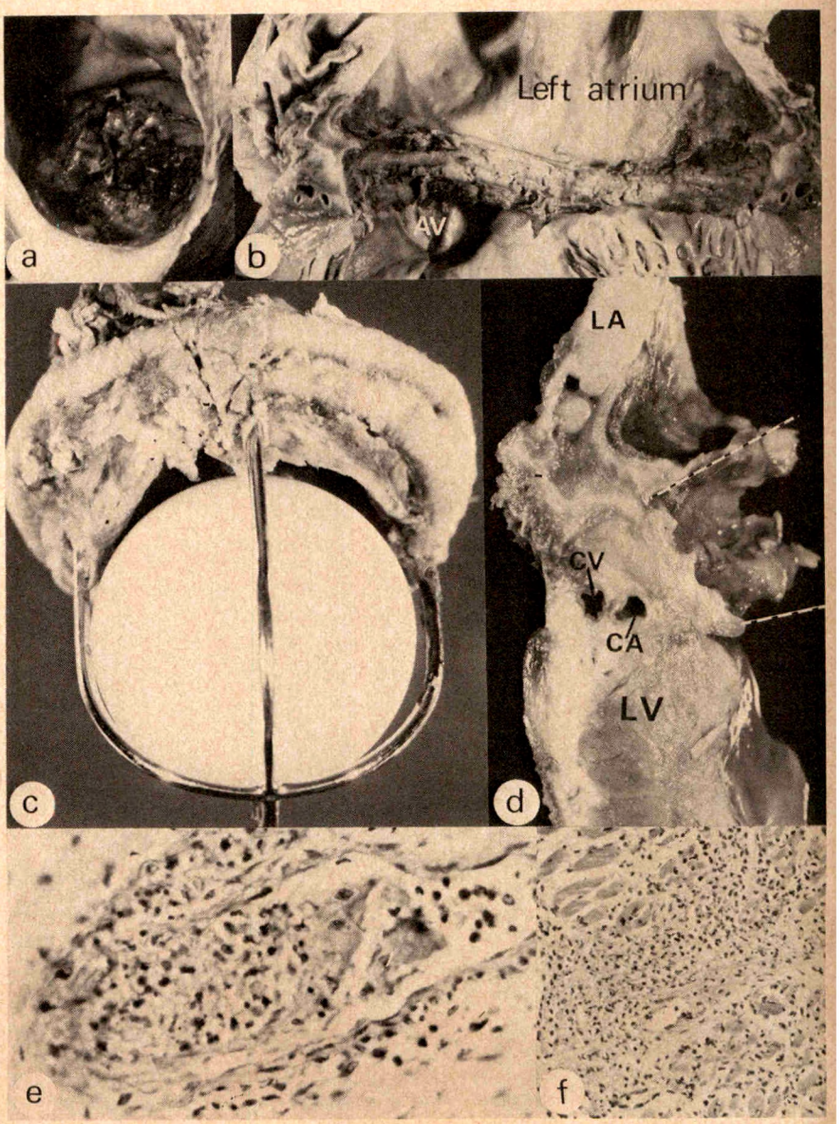

FIGURE 7. Staphylococcus aureus prosthetic mitral valve endocarditis in a 47 year old man who had the onset of symptoms of infective endocarditis 4 months after valve replacement. He had done well during the first 3 months after operation, but symptoms of infection developed after grafting of a cutaneous ulcer. Signs of prosthetic dysfunction were never detected clinically. **a,** prosthetic mitral valve orifice obstructed by vegetative material, as viewed from the left atrium. **b,** opened left atrium, mitral anulus and left ventricle after removal of the mitral prosthesis. The entire anulus is necrotic. AV = aortic valve. **c,** mitral valve prosthesis showing infected thrombus at its base. **d,** longitudinal section through the left atrium (LA), mitral anulus and left ventricle (LV). The former site of attachment of the prosthesis is designated by the **dashed lines.** The infective process burrowed through the wall of the heart and caused pericarditis. CA = coronary artery; CV = coronary vein in the right atrioventricular sulcus. **e** and **f,** hematoxylin-eosin–stained histologic sections of the left ventricle remote from the infected mitral anulus. **e,** infected embolus in an intramural coronary artery. **f,** microscopic-sized myocardial abscess. (×400 [**e**] and ×160 [**f**], reduced by 24 percent.)

patients without clinical signs of aortic regurgitation, the prosthesis was not detached at necropsy. Among patients with acute aortic regurgitation, however, classic signs of aortic regurgitation may be absent.[56–59] Signs of aortic regurgitation were not detected in three of nine necropsy patients with prosthetic aortic valve endocarditis described by Madison et al.,[44] but all three had prosthetic detachment at necropsy.

In contrast, patients with infection involving the mitral valve prosthesis usually have no clinical signs of prosthetic mitral valve dysfunction. Clinical signs of such dysfunction were not detected in any of our seven patients with prosthetic mitral valve endocarditis although the prosthesis was significantly obstructed by vegetative material in five of the seven and partially detached from the anulus in two.[12] McAllister et al.[43] reported on two patients with virtual total obstruction of the mitral prosthesis.

Morphologic Features

Valve ring abscess: The most consistent morphologic feature of prosthetic valve infection in our 22 patients was infection behind the site of attachment of the valve prosthesis, resulting in valve ring abscess. Ring abscess was present in each of our 22 patients, and in 14 the infection involved the entire circumference of the valve anulus. In several patients, however, only a portion of the circumference of the valve anulus was involved and, in one patient, histologic examination of the anulus disclosed infection that had not been apparent on gross examination. Extension of the ring infection to adjacent cardiac structures was common, especially when the aortic prosthesis was infected. This extension resulted in the frequent occurrence of both intracardiac fistulas and complete heart block or left bundle branch block. Among nine necropsy patients with prosthetic aortic valve endocarditis described by Madison et al.,[44] each had infection at the site of attachment of the prosthesis, and atrioventricular conduction defects developed in 7 (44 percent) of their entire group of 16 patients with prosthetic aortic valve endocarditis. Obviously, it is the occurrence of the infection behind the site of attachment of the prosthesis that makes reoperation so hazardous. Were the infection limited to the interior por-

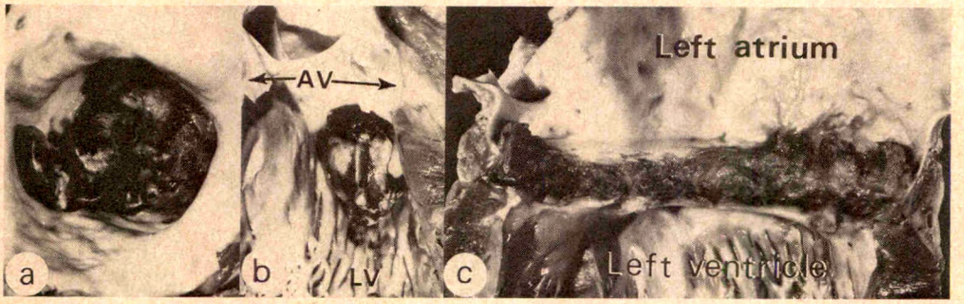

FIGURE 8. Staphylococcus epidermidis prosthetic mitral valve endocarditis in a 46 year old man who died 16 months after mitral valve replacement with a Starr-Edwards prosthesis. Eight months postoperatively, when he was asymptomatic, cardiac catheterization disclosed normal left atrial pressure and cardiac output. Signs of infection appeared 15 months after valve replacement. Despite antibiotic therapy, fatal congestive heart failure developed. **a,** mitral valve prosthesis as viewed from the left atrium. A large infected thrombus virtually occludes the mitral valve orifice. **b,** opened aorta, aortic valve (AV) and left ventricle (LV) showing infected thrombus on the cage of the mitral prosthesis. **c,** opened left atrium and ventricle showing a completely necrotic mitral valve anulus. The prosthesis has been removed.

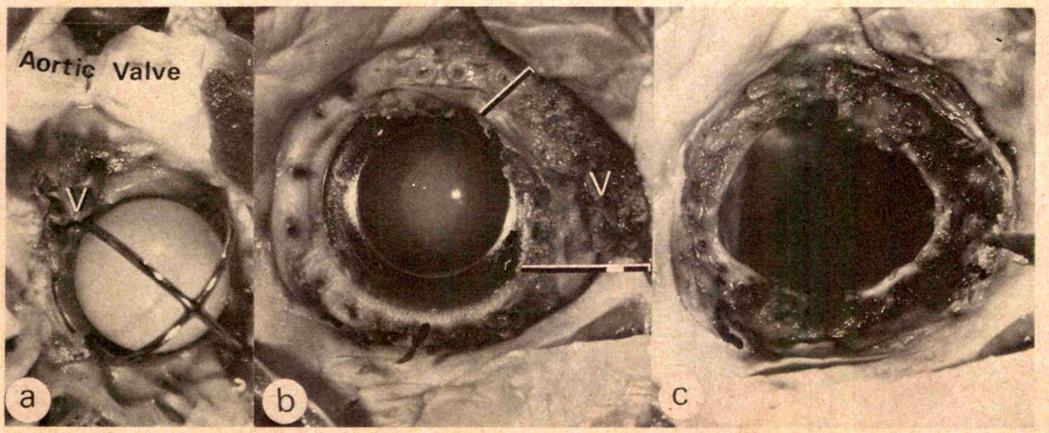

FIGURE 9. Staphylococcus epidermidis prosthetic mitral valve endocarditis in a 59 year old woman. The infection appeared 10 years after replacement of both mitral and tricuspid valves. At necropsy, only the mitral prosthesis was infected. **a,** infected mitral valve prosthesis viewed from the left ventricle. Vegetative material (V) is present on the prosthetic anulus just below the aortic valve. **b,** prosthesis as viewed from the left atrium showing vegetations (V) at the junction of the prosthetic and natural valve anuli. **c,** same view after removal of the prosthesis showing even greater extensiveness of the infection at the site of attachment of the prosthesis.

tion of the prosthesis, excision of the prosthesis should eliminate the infection. Unfortunately, as demonstrated in our patients and in those described by others,[20,35,38,43,44,47] the tissues behind the site of attachment of the prosthesis usually are involved by the infective process.

Treatment

Replacement of infected prosthesis: The occurrence of a grossly necrotic anulus at the time of reoperation for prosthetic valve endocarditis does not necessarily mean that valve replacement will be fruitless. Although it may be grossly necrotic, the anulus may be free of colonies of organisms and cultures of the necrotic anulus may be negative. In 9 of our 22 patients with prosthetic valve endocarditis and ring abscess, no stainable organisms were found in histologic sections from the prosthetic anulus.

One hazard of inserting a prosthesis in a necrotic anulus at the time of valve replacement for prosthetic valve endocarditis is burrowing of the sewing ring of the new prosthesis into the necrotic anulus with resulting impingement on movement of the poppet of the prosthesis by adjacent tissue. This sequence occurred in one of our patients and resulted in prosthetic aortic stenosis from inability of the ball to ascend in the cage (Fig. 6).

Tissue valve endocarditis: Although prosthetic valve endocarditis in patients with rigid-framed prostheses (the kind present in our 22 patients) usually indicates infection behind the site of attachment of the prosthesis, that is, the sewing ring, ring abscess may be less frequent with endocarditis involving tissue valves. Indeed, in animals and in man, the infective process may be limited to the cusps of the tissue valve, as when infective endocarditis involves natural valves.[60,61] Thus, the chance of cure, either by antibiotic therapy or valve replacement, or both, when infective endocarditis is superimposed on a homograft or heterograft (porcine valve, for example) is much better than when endocarditis involves a rigid-framed prosthesis.[61] This, then, is an advantage, although a small one, of the tissue valve (porcine) over the rigid-framed prosthesis.

Diagnosis: Establishment of the diagnosis of prosthetic valve endocarditis, particularly in the early postoperative period at times may be difficult, as pointed out by several investigators.[48,62,63] Diagnosis in the late postoperative period, in contrast, is usually

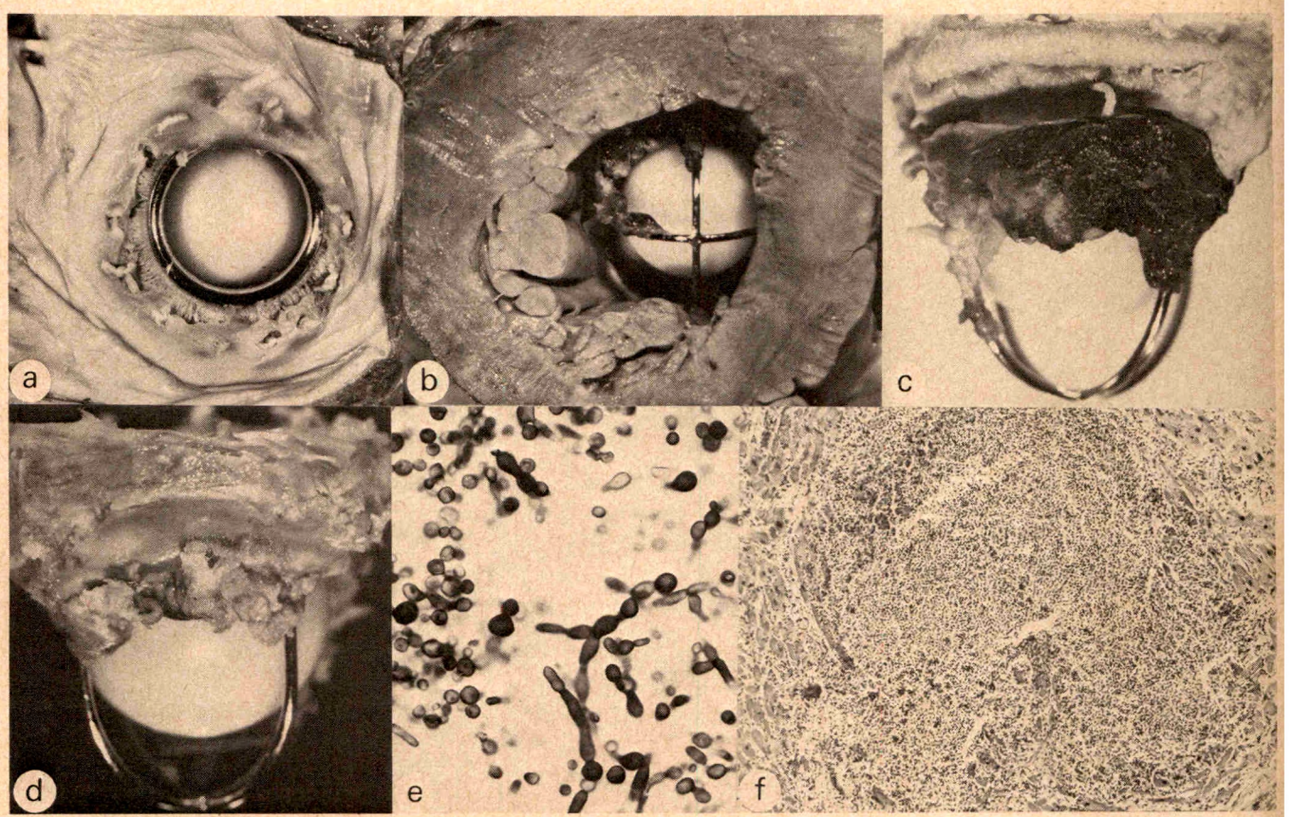

FIGURE 10. Candida species prosthetic mitral valve endocarditis in a 37 year old woman who underwent valve replacement 125 months before death because of mitral stenosis (mean mitral gradient 7 mm Hg) and regurgitation. Her tricuspid valve was replaced with a porcine xenograft because of severe tricuspid regurgitation 66 days before death. Postoperatively, she required prolonged use of a transthoracic pacing wire, which was the apparent source of the infection. She died from central nervous system embolism. Necropsy disclosed infection of the mitral valve prosthesis. **a,** mitral valve prosthesis viewed from the left atrium; **b,** prosthesis viewed from the left ventricle. Large vegetations are present on the base and struts of the prosthesis. **c** and **d,** removed mitral valve prosthesis viewed from two different sides showing large vegetations. **e,** photomicrograph of Candida species in the mitral vegetations. (Methenemine silver stain ×860, reduced by 23 percent.) **f,** photomicrograph of microabscess in the left ventricular myocardium. (Hematoxylin-eosin ×80, reduced by 23 percent.)

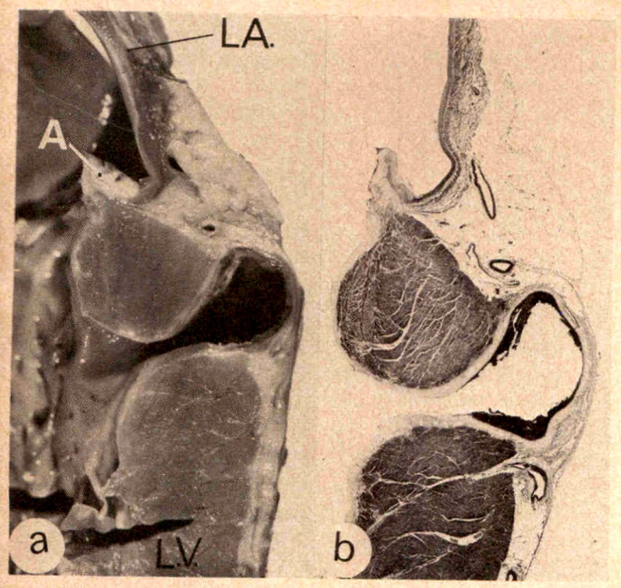

FIGURE 11. Left ventricular aneurysm simulating prosthetic valve endocarditis in a 46 year old woman. She had almost daily fever after mitral valve replacement 4 months before death and one of many blood cultures grew Staphylococcus epidermidis and diphtheroids. The clinical diagnosis was prosthetic valve endocarditis and she was treated with prolonged intravenous antibiotic therapy. She died from central nervous system embolism. At necropsy, an aneurysm was present in the basal portion of the left ventricular free wall. The prosthesis and its anulus were free of signs of infection. **a,** longitudinal cut of the left atrial (LA.) wall, mitral anulus (A) and left ventricular (L.V.) wall through the aneurysm. **b,** histologic section of the aneurysm (Movat stain). Thrombus is present in the aneurysm.

made quite readily.[48,62,63] It is worth emphasizing, however, that the combination of fever and a positive blood culture in a patient with a prosthetic cardiac valve does not always indicate the presence of prosthetic valve infection. We recently studied a patient at necropsy who was diagnosed during life as having prosthetic mitral valve endocarditis on the basis of fever, cerebral episodes consistent with emboli, and one blood culture that grew Staphylococcus epidermidis and diphtheroids. She received antibiotic treatment during most of her 4 month postoperative period and at necropsy no endocarditis was found. A left ventricular aneurysm was present immediately caudal to the mitral anulus and a sterile thrombus was present in the aneurysm (Fig. 11). The latter was the likely source of the cerebral emboli.

Antibiotic agents: There seems to be a general view that prosthetic valve endocarditis can at times be cured by antibiotic drugs. For such cure to be established, however, it is necessary that prosthetic valve endocarditis be confirmed during life, and this unequivocal confirmation can be obtained only by examination of the prosthetic valve and its anulus (site of attachment) at reoperation. In other words, to establish cure of prosthetic valve endocarditis it is necessary to be absolutely positive of the diagnosis. Although this confirmation is usually not obtained, it has now been obtained in enough patients to support the view that prosthetic valve endocarditis can indeed be cured in some patients.[16,17,21,23,24,29,30,37,39,44,45,48,64,65]

TABLE VI

Comparison between Active Infective Endocarditis (IE) Involving Prosthetic Cardiac Valves and Natural Cardiac Valves

	Mitral Valve				Aortic Valve			
	Prosthetic		Natural		Prosthetic		Natural	
	no.	%	no.	%	no.	%	no.	%
Necropsy patients (no.)	7		22		15		52*	
Age (yr) (range and average)	37–65 (52)		15–74 (43)		37–69 (54)		17–83 (45)	
Sex ratio (male:female)	3:4		12:10		13:2		41:11	
Underlying valve disease	7	100	7	32	15	100	26	50
Rheumatic	—	—	6	27	—	—	4	8
Congenital	—	—	0	0	—	—	12	23
Other	—	—	1†	5	—	—	10‡	19
None	—	—	15	68	—	—	26	50
Previous episode IE	1	14	0	0	1	7	3	6
Infecting organism								
Staphylococcus§	4	57	7	32	9	60	13	25
Alpha streptococcus	0	0	0	0	0	0	9	17
Pneumococcus	0	0	2	9	1	7	6	12
Valve regurgitation (from IE)	2	29	14	64	12	80	36	69
Valve stenosis (from IE)§	5	71	1	5	1	7	1	2
Valve-ring abscess§	7	100	1	5	15	100	21	40
Complete heart block§	0	0	1	5	5	33	4	8
Left bundle branch block§	0	0	0	0	2	13	0	0
Organ infarcts	5	71	17	77	9	60	31/47	66
Spleen >300 g	2/6	33	3	20	12	80	19/38	50

* Eighteen of the 52 also had infection of the mitral valve, but in at least 13 of them the mitral valve infection appeared to be secondary to the aortic valve infection.
† Floppy mitral valve.
‡ Degenerative (5 patients); previous infective endocarditis that healed (3 patients) and uncertain origin (2 patients).
§ $P < 0.05$.

Comparison With Endocarditis Involving Natural Valves

Comparison of observations in our 22 patients with prosthetic valve endocarditis with our observations in 74 nonsurgically treated necropsy patients with active infective endocarditis involving natural left-sided cardiac valves disclosed certain clear differences between the two groups (Table VI): (1) Ring abscess was always present in patients with prosthetic valve endocarditis regardless of the site of the prosthesis, but was present in only 30 percent of the comparison group and then, with rare exception, only when the aortic valve was infected. (2) The hemodynamic consequences were different. Prosthetic valve endocarditis caused valve obstruction nearly as often as valve regurgitation, whereas valve stenosis from active infective endocarditis involving natural cardiac valves was extremely rare.[10,66] (3) Spread of ring abscess was more extensive in patients with prosthetic valve endocarditis than in patients with natural valve endocarditis, and consequently the frequency of high grade conduction defects was much greater in the former patients. (4) The infecting organism in fatal prosthetic valve endocarditis was most commonly the Staphylococcus. Alpha streptococcus, which remains a common cause of fatal active infective endocarditis in patients with natural cardiac valves, is a rare cause of fatal prosthetic valve endocarditis.

Valve ring abscess: Among patients with infective endocarditis involving native cardiac valves, ring abscess when present almost always (95 percent of cases) involves the aortic valve.[67] Among our necropsy patients with active infective endocarditis involving a natural aortic valve, 40 percent had a valve ring abscess, whereas only 5 percent of patients with endocarditis involving a natural mitral valve had a ring abscess. In contrast, each of our 22 patients with prosthetic valve endocarditis had a ring abscess. Thus, valve ring abscess is the usual morphologic feature of prosthetic valve endocarditis, regardless of the valve infected.

Ring abscesses in patients with infection involving prosthetic valves are generally more extensive than those in patients with active infective endocarditis involving natural cardiac valves. This appears to be a consequence of the rigid nature of the prosthetic frame. Once the prosthesis is loosened by the infection, the rocking-rigid frame promotes spread of the infection. The greater turbulence across the aortic valve prosthesis probably accounts for the generally more extensive nature of ring abscess with prosthetic aortic than with prosthetic mitral endocarditis. A consequence of this extension is the greater frequency of complete heart block and left bundle branch block in patients with prosthetic aortic valve endocarditis (32 percent) than in patients with natural aortic valve endocarditis (8 percent).

Infecting organism: *Staphylococcus* (either aureus or epidermidis) is the most common cause of prosthetic valve endocarditis (59 percent). Many different organisms cause the remainder of the infections. Although alpha streptococcus was the responsible organism in 17 percent of our 74 patients with natural aortic valve infection, this bacterium was not the causative organism in any of our 22 patients with prosthetic valve endocarditis.

Valve dysfunction: The hemodynamic consequences of prosthetic valve endocarditis vary with the site of the infected prosthesis. Valve regurgitation developed in 12 of the 15 patients (80 percent) with prosthetic aortic valve endocarditis and in 2 of the 7 patients (28 percent) with prosthetic mitral valve infection. In contrast, valve obstruction developed from the infection in 5 of the 7 patients (71 percent) with prosthetic mitral valve endocarditis, and in 1 of the 15 patients (7 percent) with prosthetic aortic valve endocarditis. Among patients with natural left-sided valve infection, 65 percent (64 percent of those with mitral valve disease and 69 percent of those with aortic valve disease) had valve regurgitation from active infective endocarditis, and relatively few (3 percent) had valve obstruction from the endocarditis.[10] Thus, aortic prosthetic valve endocarditis almost always causes valve regurgitation and mitral prosthetic valve endocarditis most often causes valve obstruction.

Splenomegaly (greater than 300 g) is common both in patients with prosthetic valve endocarditis (64 percent) and in patients with native left-sided valve endocarditis (37 percent). The frequency of infarcts in other body organs is similar in both groups (64 and 70 percent, respectively).

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Echocardiogram of the Porcine Aortic Bioprosthesis In the Mitral Position

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Echocardiography was performed in 10 consecutive patients who had a clinically normally functioning porcine aortic bioprosthesis in the mitral position. Strong well defined echoes were recorded from the anterior and posterior aspects of the xenograft stent. The maximal separation of the anterior and posterior stent echoes approximated the diameter of the stent at its base. The maximal excursion of the anterior stent was 5 to 10 mm (mean 7.5) with a mean systolic slope of 15 to 35 mm/sec (mean 22.2) and diastolic slope of 11 to 59 mm/sec (mean 21.5). In all 10 patients it was possible to record an anterior xenograft leaflet with anterior movement at the onset of diastole and posterior movement at the onset of systole and with appropriately steep (more than 200 mm/sec) slopes. The diastolic (E-F) slope of the anterior leaflet in 9 of the 10 patients ranged from 9 to 38 mm/sec (mean 19). In 6 of the 10 patients a posterior xenograft leaflet with a movement pattern symmetric with that of the anterior leaflet was recorded. In two patients, the central aortic leaflet was recorded with little diastolic displacement. These two patients also had mild aortic regurgitation, which was associated with diastolic shudder of the the xenograft leaflets.

Echocardiography was also performed in one patient who was later shown to have a 10 cm^3 thrombus on the ventricular surface of a xenograft valve. The echocardiogram in this patient revealed the following abnormalities: (1) excessive anterior stent movement and systolic slope suggesting paravalvular leak in the presence of abnormal cinefluoroscopic valve tilt, and (2) multiple dense nonhomogeneous echoes between the anterior and posterior aspects of the valve stent, with an early diastolic clear space behind the anterior stent and abnormal echoes behind the posterior stent during systole. Echocardiography therefore appears to be useful in evaluating the porcine aortic bioprosthesis in the mitral position.

Recent reports indicate favorable long-term survival rates of patients with a xenograft aortic valve in the mitral position.[1] Since widespread use of such valves is possible, knowledge of their normal echocardiographic appearance will be useful.

Material and Methods

Eleven adult patients were studied consecutively. Their ages ranged from 20 to 72 years (mean 34.7). Ten patients had a clinically normally functioning flexible stented porcine aortic bioprosthesis in the mitral position and one patient had a 10 cm^3 thrombus within the valve leaflets, primarily on the ventricular side of the valve. Two of the 10 patients had mild aortic regurgitation. Ten patients were studied at least 1 month after surgical placement of the valve. The longest interval between operation and the echocardiographic study was 16 months.

All patients were thoroughly examined with a series C-100 Unirad echoscope using a 2.25 megahertz 5/8 inch (1.59 cm) diameter transducer focused at 10 cm.

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Recordings were made on a model 174 Tektronix strip chart recorder, using either heat- or light-sensitive paper. A standard M mode heart scan was performed by placing the transducer in the left parasternal interspace where the mitral valve echoes were best seen. The transducer was then rotated in a partial arc, from the mitral valve to the ascending aorta and to the cardiac apex. To record the xenograft mitral valve leaflets it was usually necessary to keep the focus on the anterior and posterior aspects of the bioprosthetic stent (Fig. 1) while slowly increasing or decreasing the gain and "sweeping" from the superolateral to the inferomedial position and back again. Since the structure (stent) that supports the leaflets resembles a cylinder when it is examined echocardiographically near its diameter, it appears as two parallel discontinuous structures that will be described as "anterior" and "posterior" stent, respectively.

Echocardiographic measurements: The diameter of the stent was measured as the distance between the anterior echoes of the anterior and posterior stent (Fig. 1). Use of the distance from the anterior echoes of the anterior stent to the posterior echoes of the posterior stent had proved an unreliable measure of stent diameter because the latter echoes often overlapped those of other structures or reverberations (Fig. 2 to 4). A range of values for stent diameter resulted from making measurements wherever the anterior and posterior stent could be defined by appropriate damping. The "true" stent diameter was obtained by subtracting 3 mm (the in vitro estimate of stent thickness) from the manufacturer's stated anulus diameter. This gave the ultrasonically detectable maximal stent diameter, located at the nadir (or base) of the stent, measured from the anterior side of the anterior stent to the anterior side of the posterior stent (Fig. 1). The maximal

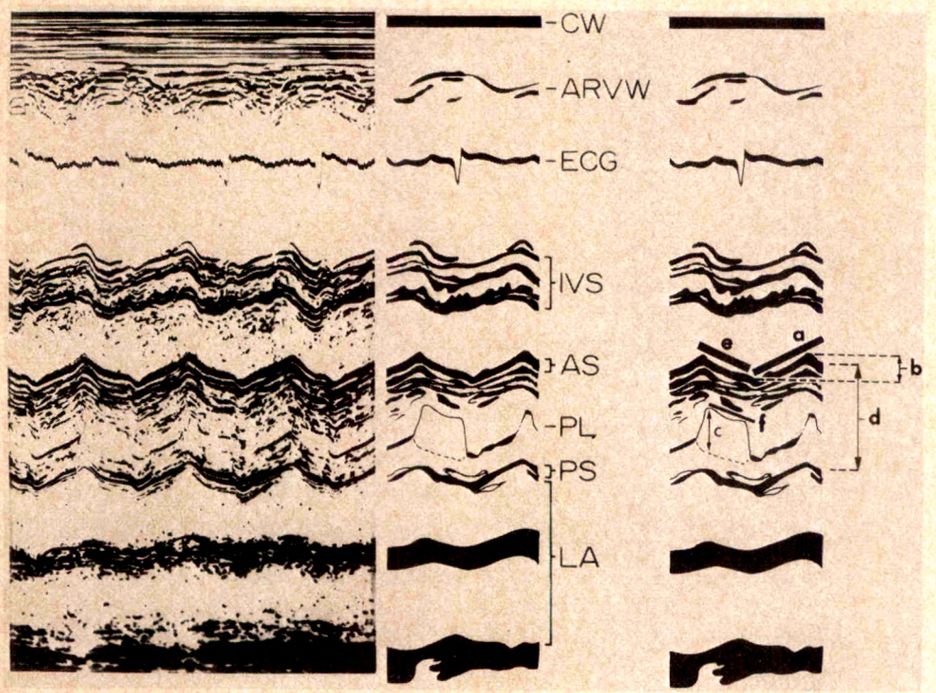


FIGURE 1. Echocardiogram of a normally functioning porcine aortic bioprosthesis in the mitral position. Linear echoes of the valve leaflets (PL) separate during diastole and reunite during systole. The diagram **(right panel)** shows how the measurements were made: a = systolic slope of the anterior stent; b = systolic excursion of the anterior stent; c = maximal diastolic leaflet separation; d = stent diameter; e = diastolic slope of the anterior stent; f = mid-diastolic closure rate (E-F slope) of the anterior leaflet. ARVW = anterior right ventricular wall; AS = anterior stent; CW = chest wall; ECG = electrocardiogram; IVS = interventricular septum; LA = left atrium; PS = posterior stent.

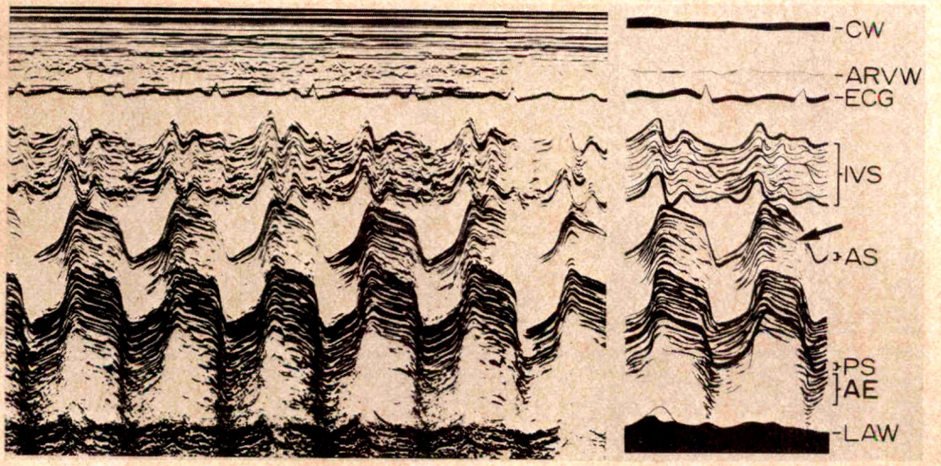
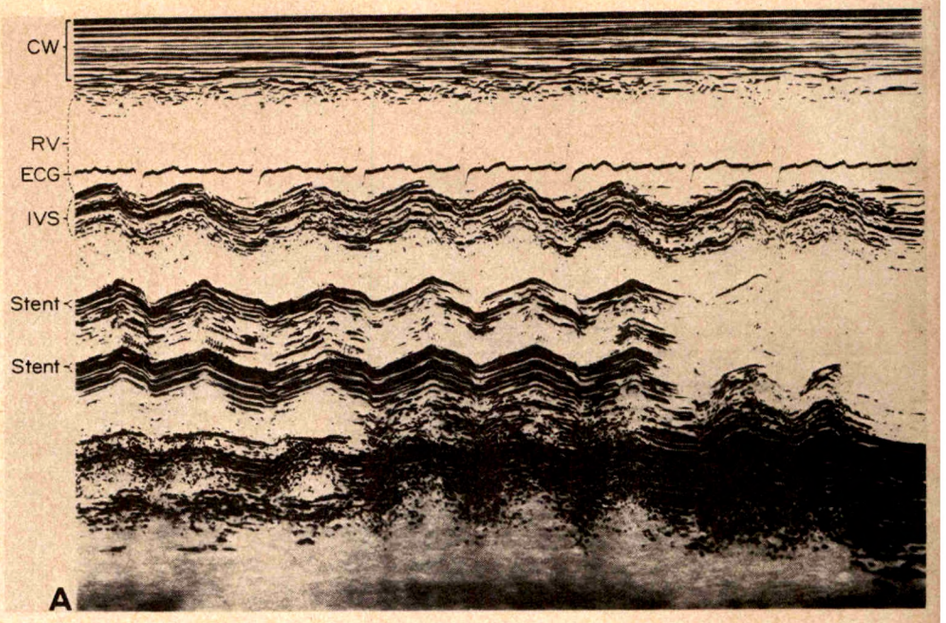
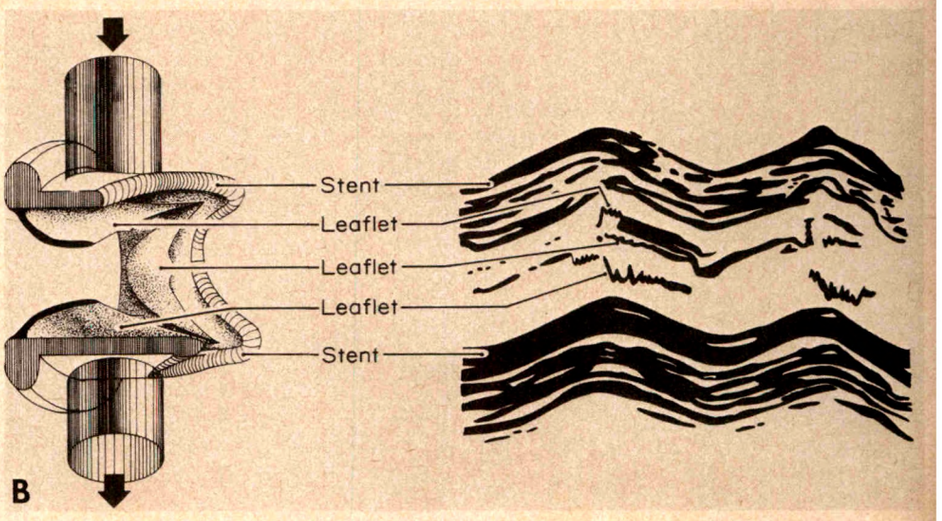


FIGURE 2. Echocardiogram of the porcine aortic bioprosthesis in the mitral position with thrombus. Multiple dense nonhomogeneous echoes are present mostly between the valve stent **(arrow).** They are most prominent behind the posterior stent during systole (AE). LAW = left atrial wall; other abbreviations as in Figure 1. •





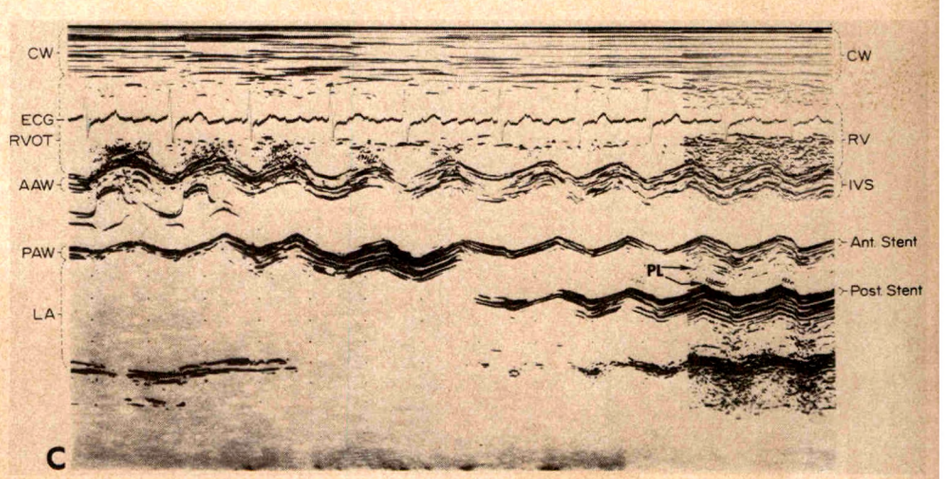


FIGURE 3. Echocardiogram of a normally functioning porcine aortic bioprosthesis in the mitral position in a patient with aortic regurgitation. **A,** left to right scan from the bioprosthesis with its three leaflets at the level of the atrioventricular junction to the left ventricular cavity. As the scan proceeds, the bioprosthetic echoes disappear abruptly. The interventricular septum moves paradoxically during systole. **B,** schematic diagram of the echocardiogram of the bioprosthesis. The **arrows** and cylinder indicate the direction and location of the ultrasonic beam as it traverses the bioprosthesis. All three leaflets are visualized in the echocardiogram, partly because of the diastolic shudder caused by aortic regurgitation. **C,** scan from the aortic root to the porcine aortic bioprosthesis in the mitral position. The posterior aortic wall (PAW) is continuous with the anterior stent. AAW = anterior aortic wall; Ant. = anterior; CW = chest wall; ECG = electrocardiogram; IVS = interventricular septum; LA = left atrium; LV = left ventricle; PAW = posterior aortic wall; PL = anterior and posterior bioprosthetic leaflets; Post. = posterior; RV = right ventricle; RVOT = right ventricle outflow tract.

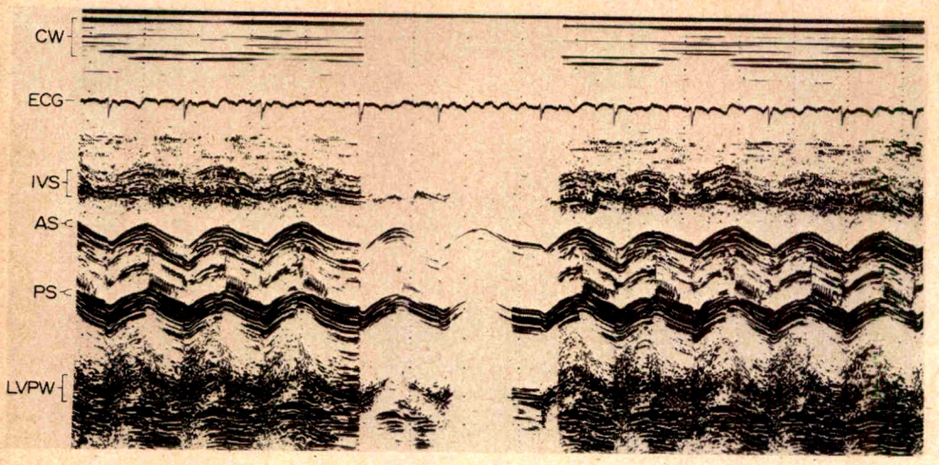


FIGURE 4. Echocardiogram of a normally functioning porcine aortic bioprosthesis in the mitral position in a second patient with aortic regurgitation. The diastolic shudder is greatest on the posterior leaflet although present on all three leaflets. During attenuation, the weaker leaflet echoes disappear before the stronger echoes of the stent. AS = anterior stent; CW = chest wall; ECG = electrocardiogram; IVS = interventricular septum; LVPW = left ventricular posterior wall; PS = posterior stent.

excursion of the anterior stent and its systolic and diastolic slopes were measured as shown in Figure 1. The slope of the anterior movement of the anterior stent during systole will be referred to as the systolic slope, and the slope of the posterior movement of this stent during diastole as the diastolic slope. Since the movements and slopes of the anterior and posterior stent were virtually identical, we have measured the anterior stent only.

The internal diameter of the stent was measured as the maximal observed distance from the posterior echo of the anterior stent to the anterior echo of the posterior stent during appropriate damping. The opening and closing slopes of the xenograft leaflets were measured. The mid-diastolic closure rate (E-F slope) of the anterior leaflet and the maximal diastolic separation of the leaflets (from their closest borders) were measured whenever appropriate visualization was obtained (Fig. 1).

Results

Stent measurements: Strong well defined echoes were always observed from the anterior and posterior stent of the normally functioning xenografts (Fig. 1). Maximal measurements of stent diameter are given in Table I. The stent diameter of the heterograft with thrombus could not be measured unless the true stent dimensions were used as a guide. When this was done, extraneous echoes were evident behind the stent during systole (Fig. 2). The maximal stent diameter measurement in eight of the nine patients with a normal prosthesis was within 2 mm (mean 1.9 mm) of the "true" stent diameter (Table I). The internal diameter of the stent ranged from 16 to 24 mm and corresponded closely with the maximal stent diameter when allowance was made for stent thickness (Table I). Maximal movement of the anterior stent ranged from 6 to 10 mm (mean 7.5). The maximal systolic slope of this stent ranged from 15 to 35 mm/sec (mean 22.2) and the maximal diastolic slope from 11 to 59 mm/sec (mean 21.5). In the patient whose xenograft had thrombus, values were abormally high for both maximal systolic anterior stent movement (21 mm) and slope (61 mm/sec). In this patient the maximal bioprosthetic valve anulus tilt along the valve's long axis was 14° as measured in successive frames of the cinefluoroscopic filmstrip.

TABLE I

Echocardiographic Measurements of the Porcine Aortic Bioprosthesis in the Mitral Position

Case no.	Stent diameter (mm) "True"* External	Stent diameter (mm) Ultrasonic External	Stent diameter (mm) Ultrasonic Internal	Anterior Stent Movement Excursion (mm)	Anterior Stent Movement Systolic Slope (mm/sec)	Anterior Stent Movement Diastolic Slope (mm/sec)
1†	20	19	16	6	19	17
2	22	24	18	6	19	15
3	24	30	18	5	15	14
4	24	22	17	8	26	22
5†	26	25	21	8	15	15
6	26	27	20	9	35	59
7†	26	24	18	6	20	15
8	28	29	24	10	26	11
9	28	29	23	7	24	34
10†	?	25	20	10	22.5	13
Mean				7.5	22.2	21.5
11†‡	33	Indefinite	21	61		26

*Derived by subtracting 3 mm from the anulus size used by the manufacturer and surgeons.

†Patients with sinus rhythm.

‡Patient with thrombus attached to inner surfaces of xenograft leaflets.

TABLE II

Ultrasonic Measurements of the Leaflets of the Normal Porcine Aortic Bioprosthesis in the Mitral Position

Case no.	Manufacturer's Anulus Diameter (mm)	Slopes of Anterior-Leaflet (mm/sec) Opening	Slopes of Anterior-Leaflet (mm/sec) E-F	Slopes of Anterior-Leaflet (mm/sec) Closing	Maximal Diastolic Leaflet Separation (mm)
1	23	266	15	354	12
2	25	329	—	>600	—
3	27	326	16	300	10
4	27	383	26	279	10
5	29	276	16	424	14
6	29	209	38	523	—
7	29	280	18	244	—
8	31	253	9	340	10
9	31	378	22	>600	—
10	?	285	13	255	—
Mean		299	19	392	11

Valve leaflet echoes: Echoes from all three valve leaflets occasionally were seen between the thick parallel lines of echoes from the circular stent. Except for timing, the excursions of the xenograft valve leaflets resembled those of the normal human aortic valve. An anterior xenograft leaflet was recorded in all 10 patients with a normally functioning bioprosthesis (Fig. 1 and 3). Opening slopes in early diastole ranged from 209 to 383 mm/sec. The E-F slopes corresponded closely with the diastolic slopes of the stent (Tables I and II), ranging from 9 to 38 mm/sec. Closing slopes in early systole ranged from 244 to more than 600 mm/sec. A posterior xenograft leaflet (Fig. 3 and 4) was recorded in 6 of the 10 patients. Five of these patients had a measurable opening slope in early diastole of 207 to 561 mm/sec. Closing slopes of the posterior leaflet in early systole, measured in three patients, ranged from 269 to more than 600 mm/sec. Maximal diastolic leaflet separation, measured in five patients, ranged from 10 to 14 mm. In the two patients with coexisting mild aortic regurgitation, a third centrally located leaflet was seen in association with moderate diastolic fluttering of all three leaflets (Fig. 3 and 4).

Xenograft with superimposed thrombus: In the patient whose xenograft had thrombus confirmed at operation, multiple dense nonhomogeneous echoes were recorded from between the anterior and posterior stent instead of the leaflets (Fig. 2).[2] In addition, a clear space just behind the anterior stent in early diastole mimicked the clear space characteristic of an atrial myxoma. A flat (4 to 11 mm thick) triangular (18 to 21 mm per side) thrombus was attached to the internal aspect of two of the leaflets, and its mobility allowed slight protrusion into the atrium only. This patient with a history of bacterial endocarditis was studied 16 months after insertion of the porcine xenograft in the mitral position. His bioprosthesis was replaced with a disc prosthesis when the thrombus was discovered.

In each patient the M mode scan from the aortic root to the porcine aortic bioprosthesis in the mitral position revealed continuity between the posterior aortic wall and the anterior stent of the bioprosthesis (Fig. 3C). During further scanning from the prosthesis toward the apex of the left ventricle, the bioprosthetic stent and leaflet echoes disappeared abruptly (Fig. 3A). Paradoxic interventricular septal motion was uniformly present (Fig. 1, 3 and 4).

Discussion

Echocardiography has been useful in evaluating normal and abnormal mitral valves and mitral valve prostheses.[3–5] It also appears to be useful in evaluating porcine aortic heterografts in the mitral position. Nonquantitative echocardiographic descriptions of the normal and at least one abnormal homograft aortic valve in the mitral position have been published.[6]

The thick parallel bands of echoes from the anterior and posterior valve stent can be simultaneously recorded with appropriate focusing and damping. Figure 3B shows the relation of the ultrasonic beam and the prosthetic valve and the resulting echocardiogram. In most patients, echocardiograms were recorded from several transducer positions, resulting in many instances in different measurements for stent diameter. In each instance the maximal diameter from any transducer position was the value used. The maximal distance between the anterior echoes from the two stent components approximated the calculated diameter at the base of the stent (Table I). Submaximal measurements were attributable to ultrasonic transection of the stent at less than the maximal diameter. The ability of the flexible stent apexes to bend inward slightly probably also contributed to making ultrasonic measurements of diameter smaller than those in vitro.[7] Since the internal diameter of the stent could be easily determined, inability to demonstrate this diameter may suggest that the stent lumen is occupied by extraneous material, as occurred in the xenograft with thrombus. The interventricular septum lies in front of the stent, and the posterior wall of the left atrium or left ventricle is behind it.

Comparison with normal aortic and mitral valves: The echocardiographic excursions of the porcine bioprosthetic valve leaflets resemble those of the normal human aortic valve.[8] The linear echoes from the porcine leaflets separate early in diastole and rejoin each other at the beginning of systole. To be recorded, they require a higher gain setting than the stent, presumably because they are less reflective than the polypropylene and Dacron® stent. The anterior xenograft leaflet was recorded in all patients with a normally functioning bioprosthesis, thus suggesting that failure to visualize this leaflet is abnormal, as in the patient with thrombus on the xenograft. It is also possible that a decrease in the uniformly rapid maximal diastolic opening and systolic closing slopes of the anterior and posterior valve leaflets indicates abnormal function, as in patients with a calcified homograft aortic valve.[6] The close correspondence of the normal anterior leaflet E-F slopes with that of the anterior stent in mid-diastole suggests that there is only slight closure of the leaflets in early and mid-diastole. This possibility is in accord with reports of a mild diastolic hemodynamic gradient even when these valves are functioning normally.[9] The maximal amplitude of diastolic leaflet separation (averaging 11 mm) could be accurately recorded in only five patients because of difficulty in adequately visualizing the posterior leaflet. The extent of valve leaflet separation of the porcine aortic xenograft during diastole is moderately less than that of either the normal human aortic valve during systole, which ranges from 16 to 26 mm,[10] or the normal mitral valve during diastole.[11] The relatively smaller leaflet separations of the normal porcine aortic xenografts may account for the mild diastolic hemodynamic gradient reported across them. Although the maximal diastolic leaflet separations show some correspondence with values for internal diameter of the stent, they aren't always proportional (Tables I and II). This may be due to lack of optimal ultrasonic beam orientation or to relative stenosis of the valve. A final conclusion should await further data.

Identification of xenograft leaflets and aortic regurgitation: The difficulty in adequately visualizing

the posterior xenograft leaflet in many patients is probably due to the obliquity of its ultrasonic beam transection with respect to the posterior stent in diastole. In both patients with aortic rugurgitation this leaflet was made apparent by diastolic shuddering (Fig. 3 and 4). The diastolic shudder due to aortic regurgitation also made the echocardiographically central (third) aortic leaflet easily identifiable. In most other patients, only two valve leaflets were well identified.

Echocardiographic scanning from the aorta to the mitral bioprosthesis revealed the continuity of the posterior aortic wall with the anterior stent. Continuing the scan to the apex of the left ventricle revealed paradoxic systolic motion of the interventricular septum, which has previously been observed in many patients with a prosthetic mitral valve. Its mechanism is uncertain, and it usually resolves within 6 months after operation.[12,13]

Identification of graft thrombus: The xenograft with thrombus was abnormal as revealed by the abnormally high values for maximal systolic anterior movement and systolic slope of the stent.[2] Normally, movement of the stent can be considered to coincide with movement of the mitral anulus, with both structures moving anteriorly during systole and posteriorly during diastole. The diastolic slopes of backward stent movement were greatest in patients with atrial fibrillation, in whom they varied inversely with the length of the R-R interval. The normal diastolic posterior slope of the anterior stent in the xenograft with thrombus makes it uncertain whether there was increased obstruction to left ventricular filling.[13]

The combination of absent leaflet echoes and dense nonhomogeneous echoes from the stent on repeated examinations suggested abnormal material such as thrombus within the stent. Additional clues to a myxoma-like mass in the space between the xenograft leaflets were the early diastolic clear space and the abnormal systolic echoes behind the anterior stent. At operation, the prosthetic valve with a thrombus on the leaflets was excised intact. The mobile thrombus protruded slightly from the atrial side of the valve. However, its attachment did not appear to allow anterior protrusion, thus making a paravalvular leak or mitral anulus aneurysm the presumed explanation for the excessive maximal anterior stent movement and slope. Since the maximal prosthetic valve tilt of 14° exceeded 12°, it strongly suggested a paravalvular leak,[14] but such a leak could not be demonstrated when the bioprosthesis was later replaced.

Acknowledgment

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Myocardial Infarction in Young Women

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This study of 24 women under age 40 years with myocardial infarction demonstrates that even in young women myocardial infarction is most commonly due to coronary atherosclerotic heart disease. Other causes of coronary occlusion were documented in 17 percent of these patients, indicating that these lesser causes of myocardial infarction are more common in young women than in older persons or in young men. In those patients with coronary atherosclerosis one or more significant risk factors could usually, but not always, be documented. The clinical manifestation of the coronary occlusion in the study group was not unlike its manifestation in groups of different ages or sex, or both.

Any review of myocardial infarction in young women must acknowledge that the disease is relatively uncommon in this patient population.[1–5] In 1947 Underdahl and Smith[4] emphasized its infrequent occurrence in women under age 40 years; they found only seven documented instances of myocardial infarction among the 95,000 women hospitalized in the Mayo Clinic during the preceding 11 years. The Framingham study[6] found that overt coronary disease occurred in only 1 in 1,000 women aged 30 to 39 years and was manifested as myocardial infarction in only 19 percent of these women. Similarly, a study of the female inhabitants of Göteberg, Sweden[7] revealed the annual incidence of myocardial infarction in women aged 35 to 38 years to be 0.03 per 1,000.

Although coronary atherosclerotic heart disease is relatively infrequent in young women, it is a leading cause of death in this group. The "Geller tables," [8] which are based on the 1960 and 1968 United States mortality experience, reveal that in black women aged 30 to 39 years coronary atherosclerotic heart disease is the most probable cause of death during the ensuing 10 years. In white women aged 35 to 39 years it ranks second behind malignant neoplasms of the breast as a cause of death.[8] It is therefore important to define the members of this group who are most prone to myocardial infarction due to coronary atherosclerosis or a less common cause. In addition, persons whose chances of having coronary atherosclerotic heart disease are small should provide a good group for studying factors other than age and sex that accelerate atherosclerosis.

Material and Methods

All material was derived from records of Grady Memorial Hospital, Crawford W. Long Memorial Hospital and Emory University Hospital for the 7 years between January 1968 and January 1975. Since this group of hospitals is composed of a large metropolitan hospital, a private community hospital and a university referral hospital, the study population was drawn from all socioeconomic conditions.

There were 49 women of 40 years of age or less among the 5,185 cases of myocardial infarction diagnosed at these three hospitals during this 7 year period. Twenty-four of these 49 women met the criteria we established for inclusion in this study, namely, a diagnosis of myocardial infarction based on the presence of chest pain characteristic of myocardial ischemia in association with one of

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the following sets of objective data: (1) new Q waves plus typical evolutionary ST-T changes in the electrocardiogram; (2) characteristic changes in the serum lactic dehydrogenase or creatinine phosphokinase levels, or both, and subsequent coronary arteriograms indicative of obstructive coronary disease; or (3) postmortem demonstration of severe coronary arterial obstruction and changes of recent myocardial infarction. Adherence to such strict criteria is not essential to the clinical diagnosis of myocardial infarction, but ensured that each patient in the study group had had an acute myocardial infarction.

Sufficient information was available in each case to establish the presence or absence of all major identifiable risk factors except blood lipids. The only lipid studies available in five patients was a single serum cholesterol value. In addition, the exact number of years of smoking or use of oral contraceptive agents could not be documented in every patient.

A patient was judged to be overweight if her body weight was more than 15 percent above the ideal weight adjusted for height. A history of hypertension was accepted if the patient reported it during the admission history or if her hospital or clinic chart indicated a diastolic pressure greater than 100 mm Hg on more than one occasion. A diagnosis of diabetes mellitus was established by an abnormal glucose tolerance test taken at least 1 month before or after the acute myocardial infarction or by documented fasting hyperglycemia (serum glucose level above 120 mg/100 ml) on multiple occasions.

Results

Etiology of Myocardial Infarction

Nonatherosclerotic coronary occlusion: Four of the 24 patients had a coronary occlusive process other than coronary atherosclerotic heart disease (Table I). In two of the four (Cases 1 and 2) embolic occlusion of a coronary artery was demonstrated at postmortem examination. Patient 1 had adenocarcinoma of the pancreas with marantic endocarditis and patient 2 had rheumatic mitral valve disease. The third patient (Case 3) had fulminant systemic lupus erythematosus; postmortem examination revealed focal areas of myocardial necrosis and hyaline thrombotic occlusion of adjacent arterioles but only minimal intimal thickening of the coronary arteries. The fourth patient (Case 4) had a massive anterior myocardial infarction rapidly followed by circulatory failure. Postmortem examination of the heart revealed an extensive acute myocardial infarction involving the entire left ventricle and septum. The only coronary arterial abnormality detected was a dissection of the media of the left main coronary artery extending into the proximal left anterior descending branch.

One additional patient (Case 5) lacked angiographic evidence of coronary occlusive process. Approximately 1 year after an acute myocardial infarction, this patient had cardiac catheterization studies that revealed decreased contractility of the apical segment of the left ventricle but entirely normal coronary arteriograms.

Atherosclerotic coronary occlusion: In the remaining 19 patients, the myocardial infarction was attributed to coronary atherosclerotic heart disease. In 12 of the 19 the coronary atherosclerosis was documented at angiographic or postmortem examination (Table I); in the remaining 7 it was assumed in the absence of evidence of another occlusive process. Nine of the 12 patients with angiographic or postmortem studies

TABLE I
Type and Site of Obstructive Coronary Lesion in 24 Young Women

Case no.	Age (yr)	Obstructive Coronary Lesion	Site of Infarction (by ECG)	Site of Obstruction
1	38	Embolic	No ECG	RCA[A]
2	15	Embolic	No ECG	LAD[A]
3	26	Arteritis	No ECG	Arteriolar occlusion[P]
4	38	Primary dissection	Anterolateral	LCA, LAD[A]
5	36	None	Anteroseptal	Normal[A], akinesia of apical segments
6	24	Atherosclerosis	Anterior	>90% proximal LAD, >90% proximal LCx[A]
7	30	Atherosclerosis	Inferior	90% mid LAD, occluded proximal RCA[A]
8	37	Atherosclerosis	Inferior	75% proximal RCA[A]
9	32	Atherosclerosis?	Anterior	
10	29	Atherosclerosis?	Anterior	>90% proximal LAD[A]
11	38	Atherosclerosis	Inferior	>90% LCx, occluded RCA[A]
12	40	Atherosclerosis	Inferior	50% LAD, 50% LCx, occluded RCA[A]
13	38	Atherosclerosis	Inferior	
14	33	Atherosclerosis?	Inferior	
15	36	Atherosclerosis?	Inferior	
16	33	Atherosclerosis	Inferior	75% proximal LAD, occluded proximal LCx, 90% proximal RCA[A]
17	40	Atherosclerosis	Inferior	
18	26	Atherosclerosis	Anterior	Occluded LAD, 90% mid-RCA[A]
19	33	Atherosclerosis?	Subendocardial	90% proximal LAD (smooth lesion)[A]
20	32	Atherosclerosis?	Inferolateral	<50% proximal RCA, <50% proximal LAD, akinesia of inferior wall[A]
21	36	Atherosclerosis?	Inferolateral	
22	34	Atherosclerosis	No ECG	90% proximal LAD, 80% proximal RCA[P]
23	38	Atherosclerosis	Inferior	
24	32	Atherosclerosis	Anterior	Occluded LAD, 90% proximal RCA[A]

? = either the appearance of the obstructive lesion or the use of oral contraceptive agents places the diagnosis of atherosclerosis in question. A = angiographic documentation of site obstruction; ECG = electrocardiogram; LAD = left anterior descending coronary artery; LCA = left main cornary artery; LCx = left circumflex coronary artery; P = postmortem documentation of site obstruction; RCA = right coronary artery.

of the coronary arteries had evidence of multiple vessel disease (Table I). The left anterior descending coronary artery was obstructed in eight patients, the right coronary artery in eight and the circumflex artery in only four. Two of the three patients with single vessel disease had an isolated smooth segmental narrowing of the proximal left anterior descending coronary artery. The electrocardiographic site of the infarction was inferior in the majority of patients (12 of 19) (Table I).

Associated Conditions

Table II indicates the presence or absence of various conditions often associated with the occlusive coronary process. Four of the 19 patients with coronary atherosclerosis had diabetes mellitus, 7 had a history of severe hypercholesterolemia (serum level 300 mg/100 ml or greater) and only 1 had a history of significant hypertension. This patient (Case 17) had had a diastolic blood pressure of 120 mm Hg or greater for 6 years. Four of the six patients (Cases 7, 9, 12 and 15) with a family history of early manifestation of coronary atherosclerotic heart disease also demonstrated one of the previously mentioned risk factors. The other two patients with such a family history had documented type IV hyperlipoproteinemia. Seven patients had a history of recent or prolonged use of oral contraceptive agents; all seven had more than one risk factor for coronary occlusive disease although a history of smoking was the only additional risk factor in two of these patients and a history of smoking plus a 1 year history of hypertension in a third patient.

Clinical Presentation

The pain was most frequently described as anterior precordial or substernal in location, and crushing or squeezing in character. Four patients had no pain in the chest but had instead pain in both arms, the left shoulder and left arm or the neck and jaw. Three patients described a sharp quality to their pain. Similar but less intense discomfort had been experienced by 14 patients before their myocardial infarction, usually within the preceding week. Of 11 patients whose activity at the time of infarction was noted, 9 had been physically inactive.

Discussion

Etiology of Myocardial Infarction

Our review indicates that even in this young age group atherosclerosis predominates as the pathologic lesion in coronary artery occlusive disease. However, the 17 percent incidence rate of other forms of coronary occlusion, suggests that the less common forms of coronary artery disease are relatively more frequent in this group than in older persons.

Coronary embolism: Two patients had coronary embolism. Although our two cases occurred in association with either rheumatic valvulitis or marantic endocarditis, previous reviews on coronary embolism have revealed that bacterial endocarditis is the underlying disease in 40 to 50 percent of the cases.[9,10] In Virchow's original description[11] of coronary embolization the patient was a young woman with bacterial endocarditis who died of myocardial infarction. Another condition predisposing to coronary embolism, the presence of a prosthetic valve, has arisen since many of the reviews on coronary embolism were completed.

Coronary vasculitis: An even less common cause of myocardial infarction found in our study is vasculitis. Coronary arteritis is usually associated with a collagen vascular disease, in particular, polyarteritis nodosa.[12] Vasculitis resulting in sufficient myocardial necrosis to be of clinical importance is quite unusual in systemic lupus erythematosus.[13–16] While cardiac involvement is common in systemic lupus erythematosus, the most

TABLE II

Associated Conditions in 19 Young Women with Coronary Atherosclerotic Heart Disease

Case no.	Family History (AMI < age 65)	Diabetes	Hyperlipidemia	Hypertension	Smoking	Overweight	Postmenopausal	Oral Contraceptive Use
6	–	+	–	–	–	–	–	–
7	+	+	–	–	–	–	–	–
8	–	+	–	–	–	+	–	–
9	+	+	–	–	–	–	–	+ (9 yr)
10	–	–	+ (c)	–	+	–	–	+ (6 mo)
11	–	–	+ (c)	–		–	+	–
12	+	–	+ (II)	–	+	+	+	–
13	–	–	–	–		+	–	–
14	–	–	+ (IV)	–	+	–	–	+ (1 yr)
15	+	–	+ (IV)	–	+	+	–	+
16	–	–	+ (IIB)	–	+	–	–	–
17	–	–	–	+	+	–	–	–
18	+	–	+ (IV)	–	+	–	–	–
19	+	–	+ (IV)	–	+	–	–	+ (3 yr)
20	–	–	–	–	+	–	–	+ (8 yr)
21	–	–	–	–	+	–	–	+
22	–	–	–	–	+	–	–	–
23	–	–	+ (IIA)	–	+	–	–	–
24	–	–	+ (II)	–	–	+	–	–

+ = present; – = absent; AMI = acute myocardial infarction; c = cholesterol greater than 300 mg/100 ml; II, IIA, IIB and IV refer to lipoprotein pattern.

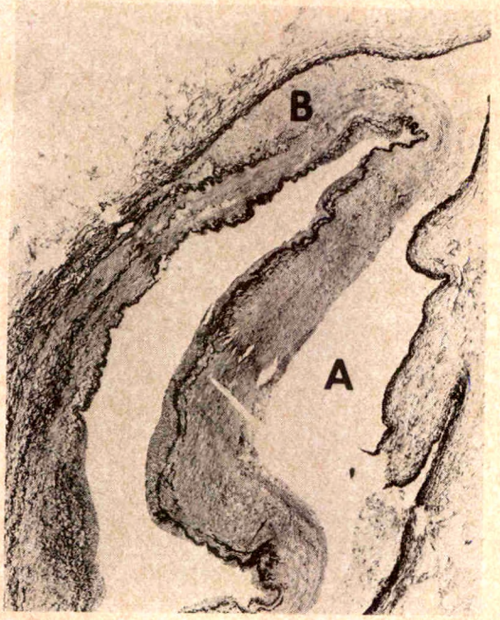

FIGURE 1. Case 4. Cross-sectional view of the left main coronary artery. Note the dissection within the media of the vessel wall (area A) and narrowing of the vessel lumen by protrusion of the intima and the inner two thirds of the media into the lumen. This bulging of the intima and media is caused by an expanding hematoma evident only in the upper portion of the dissection in this photomicrograph (area B).

TABLE III

Reports of Myocardial Infarction Occurring in Women Using Oral Contraceptive Agents*

Report	Patient's Age (yr)	Duration of Use	Site of Obstructive Lesion
Maleki and Lange[40]	29	11 mo	LAD
	38	3 yr	LAD
Naysmith[41]	33	3 yr	Not documented
Hartveit[42]	32	5 mo	Small vessels
Scharf et al.[43]	39	6 mo	Not documented
Dear and Jones[44]	27	4 yr	LAD
	37	1 yr	LAD
Wardekar et al.[45]	29	15 mo	LAD
Waxler et al.[46]	27	. . .	LAD
	35	. . .	LAD
	29	. . .	LCx
Weiss[47]	32	1 yr	AS-MI
	28	1 yr	LAD

* The patients included in the studies by Oliver[48] and Radford and Oliver[49] are not included because the site of the lesion was not documented. Eleven of their 16 patients had an anterior infarct and the average duration of use of oral contraceptive agents was 3.5 years.

AS-MI = anteroseptal myocardial infarction (no anatomic or arteriographic data given for this patient); LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery.

common site of involvement is the pericardium and second the endocardium.

Dissecting aneurysm of coronary arteries: This cause of myocardial infarction occurs primarily in young women.[17–20] There was one case in our series. This condition is characterized by the presence of a hematoma within the media of these small caliber vessels resulting in luminal obstruction (Fig. 1). A review of the 43 previously reported cases revealed that 32 of the patients were women, including 19 less than 40 years of age; 12 of these patients were in the peripartal period. Although our patient was not peripartal, she had been receiving large doses of estrogen by pellet implantation. In 37 of the 43 previously reported cases, the dissection involved a single coronary artery. The left anterior descending artery was the site of dissection in 30 of these 37 cases. Twenty-seven patients died suddenly, whereas the other patients survived several hours to 2 weeks.[20]

Associated Conditions Predisposing to Premature Atherosclerosis

Risk factors: Just as the uncommon causes of myocardial infarction are usually associated with the presence of a predisposing state, certain conditions have been incriminated as contributors to the development of premature coronary atherosclerosis. Several studies[4,21–26] have suggested that myocardial infarction is infrequent in young women who do not have a strongly positive family history, diabetes, hypertension, hyperlipidemia or obesity or are not in the postmenopausal state. Other investigators have noted that compared with women in the general population, women with myocardial infarction are more likely to smoke,[6,27] tend to have more pregnancies,[6,28] more often have personality traits such as aggression and neurotic self-assertiveness[6] and are more likely to be physically inactive.[6,29] In addition, various prospective epidemiologic studies[30–33] have associated obesity, diabetes, hypercholesterolemia and smoking with the development of coronary atherosclerosis. In recent years several angiographic studies have evaluated coronary risk factors in young women. Heinle et al.[34] found either an abnormal lipoprotein pattern or an abnormal glucose tolerance test in 96 percent of their female patients under age 50 years with angiographic evidence of coronary obstructive disease. In their coronary angiographic study, Salel et al.[35] reported that no woman under age 50 years had coronary disease in the absence of hyperlipoproteinemia, abnormal glucose tolerance or hypertension.

Lipid abnormality: Eleven of our 19 patients with coronary atherosclerosis had a documented lipid abnormality. Eight of these patients had severe hypercholesterolemia (greater than 300 mg/100 ml), including one whose cholesterol was elevated as a feature of the nephrotic syndrome. Four of the eight patients without a lipid abnormality had diabetes mellitus; in two of the four the diabetes became apparent very early (before age 6 years).

Our study does not resolve the question of whether surgical castration results in precocious atherosclerosis,[36,37] since our patients with a history of castration had severe hypercholesterolemia. Perhaps the castration contributes to the lipid abnormality, as suggested by Oliver and Boyd.[38]

Hypertension: Only one of our patients had significant hypertension. Our inability to establish a close

correlation between the presence of hypertension and the development of coronary atherosclerotic heart disease is substantiated by the studies of Heinle et al.[34] and Salel et al.[35] Similarly, the Tecumseh study[39] found no increased incidence of hypertension in women with ischemic heart disease until after age 60.

Oral contraceptive agents: Seven of the patients in this study were using oral contraceptive agents at the time of, or shortly before, their myocardial infarction. In recent years there have been reported an increasing number of cases of young women who had acute myocardial infarction while using these agents.[40–47] Table III lists the reported cases in which the site of the occlusive lesion was identified. With a single exception, the occlusive coronary lesion has been a discrete segmental occlusion of a branch of the left coronary artery associated with otherwise normal vessels. In our study the two patients using oral contraceptive agents evaluated by angiography had a similar smooth-walled segmental obstruction of the anterior descending branch of the left coronary artery (Fig. 2). Although an isolated coronary obstructive lesion can occur in patients not taking oral contraceptive agents and the data are not conclusive evidence linking these agents to myocardial infarction, like previous investigators, we are intrigued by this finding. It is also interesting in this regard that the only patient in our series who experienced a systemic embolus was taking an oral contraceptive agent.

All of our patients using oral contraceptive agents had an additional risk factor for coronary arterial obstructive disease. This observation was also made in three other studies[48–50] concluding oral contraceptive use was more frequent in women experiencing myocardial infarction than in age-matched control groups. However, one other study[51] concluded that oral contraceptive agents exerted an effect independent of other risk factors. Prolonged use of oral contraceptive agents appears from all these studies to heighten the risk of myocardial infarction.

Myocardial infarction and normal coronary angiogram: Finally, we must explore the enigma that exists in Patient 5, who had irrefutable objective evidence of myocardial infarction and a normal coronary angiogram. This particular problem first came to medical attention in the United States in 1910 with William Osler's description[52] of a young man who had recurrent angina pectoris for several years, but on postmortem examination had normal coronary arteries. In spite of the confusion caused by the tendency of some angiographers to place any patient with chest pain and normal coronary arteriograms into this category, there is clearly a group of patients who have normal coronary arteriograms and yet have objective evidence of myocardial ischemia.[53–57] A few of these patients have died and on postmortem examination had evidence of subendocardial infarction in spite of normal coronary arteries and arterioles.[54] This paradoxic condition is most common in young women.[53,54,56] Moreover, in most of the patients, as in our patient, there has been no strong correlation with either abnormal serum lipoprotein patterns or glucose intolerance.

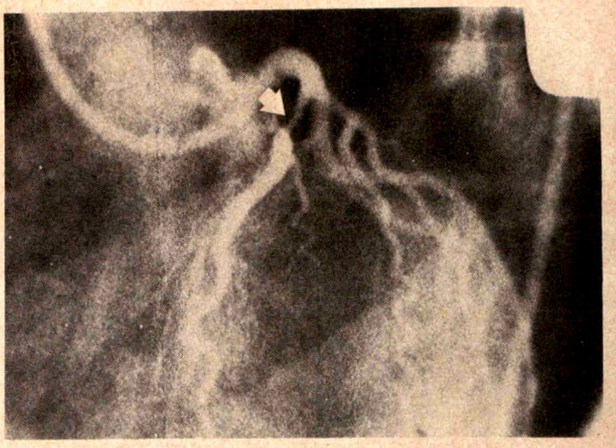

FIGURE 2. Case 19. Left anterior oblique view of the selective left coronary arteriograms. The **arrow** points to a long smooth segmental obstruction of the proximal portion of the left anterior descending artery as the only site of arterial obstruction in this patient.

Clinical Presentation

Our study indicates that the clinical presentation of myocardial infarction in this group of patients is not unlike that in other groups. The pain in these young women usually fits the classic description of pain associated with myocardial infarction. A previous review[58] has likewise emphasized the typical character of the pain associated with myocardial infarction in young adults. Fourteen of our 19 patients with atherosclerotic coronary occlusion had previously experienced chest pain similar to that associated with their myocardial infarction. The pain preceding the infarction had usually occurred during exertion, whereas the pain associated with the infarction commonly developed at rest. A frequent pattern in our patients appeared to be the development of exertional chest pain several hours to days before their infarction, with only three instances of a history of chest pain exceeding 1 month.

Conclusion

Our results indicate that the predominant occlusive process in young women (age 40 years and under) experiencing myocardial infarction is coronary atherosclerosis. However, the 17 percent incidence rate of the less common causes of coronary occlusion suggests that such causes are relatively more common in this age group than in others. Our findings indicate that most young women with overt coronary atherosclerotic heart disease have a detectable coronary risk factor but that myocardial infarction can occur in a young woman who has no major risk factor. Finally, myocardial ischemia in this segment of our population appears to manifest itself in a manner similar to that seen in the population as a whole.

Acknowledgment

We thank the many physicians who participated in the care of the patients in our study group. We especially thank Drs. Linton Bishop, Barry Silverman, Tom Bailey and John Oak.

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Reappraisal of the Functional Significance of the Coronary Collateral Circulation

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A review of data in 465 patients with complete obstruction of either the left anterior descending or right coronary artery was undertaken to evaluate the functional role of the collateral circulation. Complete obstruction of a dominant right coronary artery was observed in 288 patients, 83 percent with distal filling and visualization of the posterior descending artery by way of collateral vessels. Complete obstruction of the left anterior descending artery was noted in 177 patients, 71 percent with filling and visualization distal to the obstruction by way of collateral vessels. Among patients with obstruction of the left anterior descending artery, there was a significantly greater frequency of congestive heart failure and cardiomegaly in those without collateral vessels than in those with collateral vessels. The former also had a significantly greater frequency of both electrocardiographic evidence of an anterior wall myocardial infarction and angiographic findings of anterior wall asynergy. The frequency of inferior myocardial infarction and inferior wall asynergy was not influenced by the presence of collateral vessels. These observations indicate that the collateral circulation plays a significant protective role in the presence of obstruction of the left anterior descending artery, which is not apparent with obstruction of the right coronary artery.

The functional significance of the coronary collateral circulation has been evaluated by many investigators.[1–19] Intercoronary anastomoses are present in all normal human hearts[6] but are not angiographically demonstrable except in the presence of coronary artery disease.[7] Coronary collateral vessels are commonly present in coronary artery disease and are related to the extent and severity of the vascular disease.[1,3,8,9] In spite of the ubiquitous nature of the collateral circulation in severe coronary artery disease, most investigators have failed to prove any beneficial effect from these vessels.[1–4,14–16] However, several reports do suggest that collateral vessels may have a protective role against myocardial dysfunction[10,11,17–19] and may be accompanied by longer survival.[12,13] We recently reviewed our experience in a large group of patients with complete obstruction of either the left anterior descending or right coronary artery to determine whether the presence or absence of collateral vessels to these arteries has a protective role. The resting electrocardiogram and the contractile pattern of the left ventricle were utilized to evaluate the role of coronary collateral vessels in these patients.

Methods

A review of the experience at this institution revealed 465 patients with complete obstruction of either a dominant right coronary artery or the left anterior descending artery. All patients were referred because of symptomatic coronary artery disease. Routine history and physical examination were performed in each patient. Radiologic interpretation was performed by a radiologist to define the presence or absence of cardiomegaly. A 12 lead standard electrocardiogram was obtained in all patients. The electrocardiographic diagnosis of

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inferior or anterior myocardial infarction was based on accepted criteria.[20] In the coding of various patterns of infarction, no distinction was made between anteroseptal, anterior and anterolateral myocardial infarction; all three types were combined under the heading of anterior myocardial infarction. Not included in this study were patients with left bundle branch block since this finding might obscure the electrocardiographic evidence of either inferior or anterior myocardial infarction.

Selective coronary arteriography was performed in multiple projections using either the Judkins or the Sones method. Complete obstruction of a dominant right coronary artery was observed in 288 patients. A dominant right coronary artery was presumed in the presence of complete proximal obstruction of the right coronary artery when the left coronary artery did not give rise to the posterior descending artery or if collateral vessels filled a posterior descending artery that was not an extension of the circumflex artery. Complete obstruction of the proximal left anterior descending coronary artery was observed in 177 patients. These 465 patients with complete proximal obstruction of the left anterior descending or right coronary artery form the basis of this report. Not included were the unusual instances of complete obstruction of both of these arteries or cases of significant main left coronary artery disease. Criteria for the presence of significant coronary collateral vessels, either intra- or intercoronary anastomosis,

TABLE I

Clinical Profile in Relation to the Presence or Absence of Collateral Vessels

	Obstruction of Right Coronary Artery		Obstruction of Left Anterior Descending Artery	
	Without Collaterals	With Collaterals	Without Collaterals	With Collaterals
Cases (no.)	44	244	52	125
Age (yr) (mean ± 1 SD)	51 ± 8	52 ± 13	52 ± 7	50 ± 9
Duration of symptoms (yr) (mean ± 1 SD)	3.6 ± 2.9	4.0 ± 4.1	3.6 ± 3.7	3.9 ± 3.8
Hypertension	13 (30)	84 (35)	14 (27)	36 (29)
Myocardial infarction (by history)	31 (70)	130 (54)	48 (92)*	51 (41)*
Congestive heart failure	5 (11)	16 (7)	11 (21)†	9 (7)†
Diabetes mellitus	6 (14)	26 (11)	5 (10)	11 (9)
Cholesterol (≥300 mg/100 ml)	3 (7)	24 (10)	6 (12)	10 (8)
Triglyceride (>160 mg/100 ml)	15 (34)	70 (29)	18 (35)	38 (30)
Cardiomegaly	16 (36)	50 (21)	24 (46)*	20 (16)*

Numbers in parentheses indicate percent of total number.
* $P < 0.005$ (patients with and without collateral vessels).
† $P < 0.01$ (patients with and without collateral vessels).
SD = standard deviation.

TABLE II

Collateral Circulation in Relation to Electrocardiographic Evidence of Anterior and Inferior Transmural Myocardial Infarction and Abnormal Left Ventricular Contractile Pattern of Anterior and Inferior Walls

	Cases (no.)	ECG Evidence of Infarction (no. [%])	Abnormal Contractile Pattern (no. [%])
A. Inferior Wall			
Obstructed right coronary artery			
With collaterals to this artery	240	127 [53]	160 [67]
Single vessel disease	29	17 [59]	17 [59]
Double vessel disease	79	38 [49]	49 [63]
Triple vessel disease	133	72 [54]	95 [71]
Without collaterals to this artery	44	29 [66]	36 [82]
Single vessel disease	8	8 [100]	6 [75]
Double vessel disease	14	8 [57]	12 [86]
Triple vessel disease	22	13 [59]	18 [82]
B. Anterior Wall			
Obstructed left anterior descending coronary artery			
With collaterals to this artery	125	42 [34]	83 [66]
Single vessel disease	39	11 [28]	22 [56]
Double vessel disease	48	19 [40]	38 [79]
Triple vessel disease	38	12 [32]	23 [61]
Without collaterals to this artery	52	44 [85]	48 [92]
Single vessel disease	12	11 [92]	11 [92]
Double vessel disease	24	20 [83]	24 [100]
Triple vessel disease	16	13 [81]	13 [81]

Numbers in brackets represent percent of total number.
ECG = electrocardiographic.

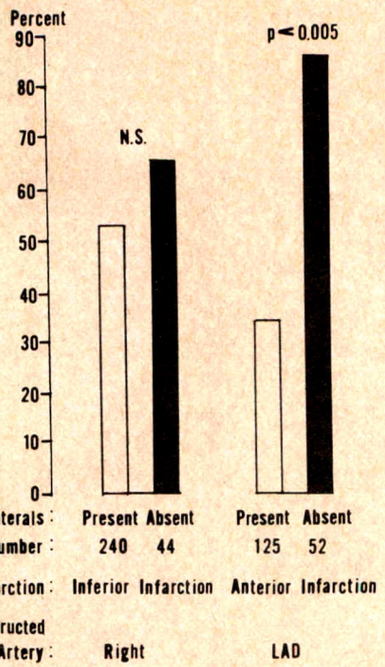

FIGURE 1. Frequency distribution of an electrocardiographic (EKG) pattern of infarction for a completely obstructed right coronary artery **(left)** and a completely obstructed left anterior descending artery (LAD) **(right).** The frequency of an inferior myocardial infarction is not influenced by the presence **(white bar)** or absence **(black bar)** of collateral vessels, whereas the frequency of an anterior infarction is significantly greater in patients without than in those with collateral vessels (pair of bar graphs at right). N.S. = not significant; p = probability.

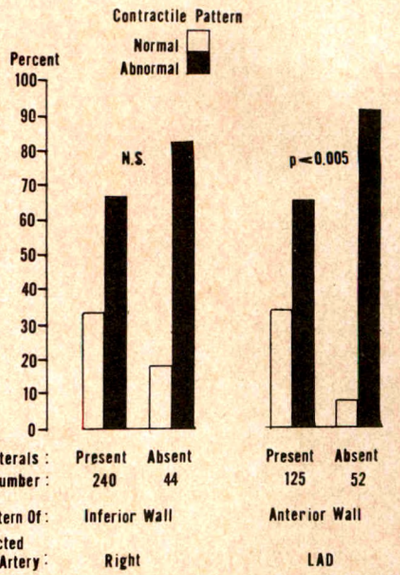

FIGURE 2. Frequency distribution of the contractile pattern of the inferior wall **(left)** and the anterior wall **(right)** depending on the presence or absence of collateral vessels to the right coronary artery and left anterior descending coronary artery (LAD), respectively. The frequency of a normal contractile pattern **(white bar)** or an abnormal pattern **(black bar)** of the inferior wall is not influenced (N.S. = not significant) by the presence or absence of collateral vessels to an obstructed right coronary artery. The frequency of a normal contractile pattern **(white bar)** of the anterior wall is significantly greater in the presence of collateral vessels to the left anterior descending artery.

required visualization of the posterior descending artery in the presence of complete proximal right coronary arterial obstruction or visualization of the left anterior descending artery in the presence of complete proximal obstruction of this vessel. These criteria are somewhat different from those of others[3,4,14,16] since we required visualization of the major trunk of the occluded vessel. Others have accepted subtotal obstruction of vessels and visualization of accessory blood vessels subserving an area of myocardium distal to the occluded vessel. Significant coronary artery disease was defined as narrowing of a coronary artery by more than 50 percent of the wall lumen.

Left ventricular angiograms were performed in the right anterior oblique projection and analyzed for localized or diffuse abnormalities of contraction involving the anterior or inferior wall by methods previously described.[21] These methods include qualitative evaluation for determining localized contractile abnormalities as well as quantitative evaluation of the transverse hemiaxis and the long axis. Determination of the anterior transverse hemiaxis and long axis were utilized to evaluate the anteroapical wall, whereas the inferior transverse hemiaxis was utilized to evaluate the inferior wall. An abnormal segmental contractile pattern required qualitative or quantitative evidence of segmental contractile dysfunction. Anterior or inferior asynergy was considered present if the respective mid-hemiaxis revealed less than 30 percent shortening. Using these criteria, we noted agreement between the qualitative interpretation and quantitative findings in the majority of patients. However, in almost 20 percent we interpreted the left ventricular angiogram as demonstrating qualitatively localized contractile abnormalities although the criteria for asynergy were not met by the quantitative method. In such instances the patient was still considered to have localized contractile abnormalities. Elimination of such cases had no effect on the final results.

Statistical significance of the data comparing patients with and without collateral vessels was analyzed using chi square analysis.

Results

Right coronary arterial obstruction: Among 288 patients with complete obstruction of the right coronary artery, collateral vessels to the distal portion of this vessel were observed in 244 (87 percent). There were no significant differences in age, duration of symptoms or frequency of hypertension, diabetes mellitus or abnormal serum cholesterol or triglyceride levels in patients with and without collateral vessels. The frequency of a history of myocardial infarction, congestive heart failure or cardiomegaly was not significantly influenced by the presence or absence of collateral vessels (Table I).

The influence of collateral vessels on the prevalence of electrocardiographic evidence of a transmural myocardial infarction is given in Table II. In the presence of an obstructed right coronary artery, inferior myocardial infarction was observed in 53 percent of the patients with collateral vessels, a frequency not significantly different from that in patients without collateral vessels (Fig. 1). The frequency of single, double and triple vessel disease was essentially similar in patients with and without collateral vessels. All patients with isolated obstruction of the right coronary artery without

collateral vessels had electrocardiographic evidence of an inferior myocardial infarction as contrasted to 59 percent of those with collateral vessels ($P < 0.05$). However, in patients with double or triple vessel disease and an obstructed right coronary artery, the frequency of electrocardiographic evidence of a transmural inferior myocardial infarction was not influenced by the presence of collateral vessels (Table II). The presence of collateral vessels to an obstructed right coronary artery did not significantly influence the contractile pattern of the inferior wall of the left ventricle (Fig. 2). Evaluation of the data on the basis of the number of vessels involved with significant disease revealed no influence of collateral vessels on the left ventricular contractile pattern (Table II).

Left anterior descending arterial obstruction: In the 177 patients with complete obstruction of the left anterior descending artery, collateral vessels distal to the obstruction were observed in 125 (71 percent). There were no significant differences in age, duration of symptoms or frequency of hypertension, diabetes mellitus or abnormal blood lipid levels. The frequency of a prior myocardial infarction ($P < 0.005$), congestive heart failure ($P < 0.01$) and cardiomegaly ($P < 0.005$) was significantly greater in patients without collateral vessels (Table I).

The frequency of electrocardiographic evidence of an anterior myocardial infarction was significantly ($P < 0.005$) greater in the patients without than in those with collateral vessels (Fig. 1). The frequency of single, double and triple vessel disease was essentially similar in the patients with and without collateral vessels. The frequency of an anterior myocardial infarction in the patients with an obstructed left anterior descending artery was independent of the number of vessels involved with significant coronary artery disease and was influenced only by the presence or absence of collateral vessels (Table II). The frequency of an abnormal contractile pattern of the anterior wall of the left ventricle was significantly ($P < 0.005$) greater in the absence of collateral vessels (Table II). This greater frequency was not altered by taking into account the number of vessels involved with significant coronary artery disease.

Discussion

The review of our case material was stimulated by observations made in two patients with complete obstruction of the main left coronary artery. In both cases the electrocardiogram failed to demonstrate any evidence of a prior myocardial infarction, and the left ventricular angiogram revealed only minimal impaired movement of the anterior wall in one patient and a normal contractile pattern in the other. In both cases, selective angiographic study revealed a normal right coronary artery giving rise to extensive collateral vessels with opacification of both the left anterior descending and circumflex coronary arteries. Thus, in these two patients, the collateral circulation appeared to have some protective function, although stress testing in both revealed ischemic S-T segment depression of more than 2 mm. This finding indicates, as suggested by Blumgart et al.,[22] that collateral vessels are able to maintain resting requirements of the heart but not the demands of increased work load. Thus, the failure of others[1–4,9,15,23,24] to observe any effect of collateral vessels on physical work capacity or response to exercise stress testing would not negate the protective function of collateral vessels. These observations indicate only, as observed in the dog by Kattus and Gregg,[25] that collateral vessels are unable to meet the increased myocardial oxygen needs that physical activity demands.

One difficulty in evaluating the functional significance of the collateral circulation is that the angiographic methods now utilized do not give quantitative information about the blood flow in these vessels. Quantitative estimation of the number and size of collateral vessels[14,17] is subjective and does not necessarily reflect their function. Furthermore, the resolving power of angiographic equipment limits identification to vessels of 100 μ or more in diameter.[7] In our study, we required for identification of significant collateral vessels visualization of the major trunk distal to the obstruction. In the case of the right coronary artery, we required opacification of the distal portion, including the posterior descending artery. For the left anterior descending coronary artery, we required visualization of this artery distal to the obstruction. This may in part explain the difference in our results from those in prior reports.[2,3,4,14] Some investigators[3,4] included patients in their study if accessory blood vessels were visualized in areas of the myocardium distal to the occluded vessel. Such a situation is not comparable with visualization of the native coronary blood vessel distal to the obstructed area. Furthermore, to evaluate comparable lesions, we included only patients with *complete* obstruction of a main coronary artery, either the right or left anterior descending artery, whereas others[1–3,14,16,17,23] have included patients with subtotal obstruction of these vessels. Thus, in our study, we compared patients with similar lesions who differed only in the presence or absence of collateral vessels supplying the major distal trunks.

Role of collateral vessels in anterior versus inferior infarction: Prior studies[26,27] have demonstrated a good correlation between abnormal Q waves in the electrocardiogram indicative of a transmural myocardial infarction and localized abnormalities of the left ventricular contractile pattern. These studies have also revealed a good relation between localization of the infarction as defined by the electrocardiogram and the coronary anatomy as defined by selective coronary arteriography. Thus, anterior myocardial infarction has been associated with both significant disease of the left anterior descending artery and anterior wall asynergy of the left ventricle, whereas electrocardiographic evidence of inferior myocardial infarction is correlated with significant disease of the right coronary artery and inferior wall asynergy of the left ventricle. On the basis of these previous observations we examined the role of the coronary collateral circulation in our select group of patients demonstrating complete obstruction of either the left anterior descending or right coronary artery. A comparison was made in each group of patients to evaluate whether the frequency of transmural infarction

and abnormal left ventricular contractile pattern was different in patients with and without collateral channels to the obstructed artery.

Our results (Table II, Fig. 1) indicate that the collateral circulation has a protective role against anterior myocardial infarction in a significant number of patients with a totally obstructed left anterior descending coronary artery. This apparent protective effect was further established by evaluating the left ventricular contractile pattern (Table II, Fig. 2) in this group. Complete obstruction of the left anterior descending artery was associated with a normal anterior wall contractile pattern in only 8 percent of patients without collateral channels as contrasted to 34 percent of patients with collateral channels. These findings may explain the increased frequency of congestive heart failure and cardiomegaly (Table I) in patients without collateral channels to this artery.[28] Taking into consideration the number of vessels involved with significant disease in no way altered the apparent beneficial effect of collateral vessels in both the electrocardiographic and left ventricular contractile patterns in these patients. In contrast, patients with obstruction of the right coronary artery demonstrated no beneficial effect from collateral circulation, as evidenced in either the electrocardiogram (Table II, Fig. 1) or left ventricular angiogram (Table II, Fig. 2), unless their disease was limited to the right coronary artery alone. The lack of a protective role of collateral vessels in the group with an obstructed right coronary artery in the angiographic study may in part be due to methodology, since the single plane angiographic technique does not permit appreciation of the posterolateral wall of the left ventricle. Furthermore, involvement of the contralateral coronary artery may limit collateral flow through intercoronary anastomosis. This possibility is suggested by the findings in the patients with isolated obstruction of the right coronary artery whose intercoronary collateral flow was not impaired by disease of the donor vessel. Among patients with isolated obstruction of the right coronary artery all of those without collateral vessels had evidence of an inferior myocardial infarction compared with only 59 percent of those with collateral vessels.

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Effect of Glucose-Insulin-Potassium Infusions on Arteriovenous Differences of Glucose and of Free Fatty Acids and on Tissue Metabolic Changes in Dogs With Developing Myocardial Infarction

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Glucose-insulin-potassium infusions were given to dogs for 6 hours, starting 30 minutes after ligation of the left anterior descending coronary artery. Effects on substrate arteriovenous differences, indexes of ischemic damage and other tissue metabolic changes were compared with changes in dogs with comparable ligations but no infusions. Glucose-insulin-potassium increased the arteriovenous difference of glucose, decreased that of free fatty acid and decreased the arterial free fatty acid/albumin molar ratio. Glucose-insulin-potassium accelerated the rate of fall of the epicardial S-T segment in the infarct zone and prevented the small rise in S-T segment found in the periinfarct and nonischemic zones. Glucose-insulin-potassium increased the tissue content of glycogen in peripheral infarct, periinfarct and nonischemic zones; increased tissue potassium ion/sodium ion ratios in epicardial infarct zones and in the periinfarct zone; increased adenosine triphosphate in the endocardial infarct zone; decreased inorganic phosphate in the periinfarct and nonischemic zones and in the endocardial infarct zone; and increased lactate in the central infarct and nonischemic zones. The phosphate potential increased in the periinfarct and nonischemic zones. Thus, many glucose-insulin-potassium effects were greater in the peripheral infarct and especially the periinfarct zones. Although increased anaerobic metabolism with lactate production could not be excluded as a mode of action of glucose-insulin-potassium, estimated rates of anaerobic glycolysis were very low, suggesting that other effects such as increased aerobic glycolysis decreased extraction of free fatty acid by the heart, increased tissue glycogen or a "membrane" effect might be of major importance.

Theoretical arguments have been advanced to suggest that increased rates of glucose metabolism and glycolysis could help promote survival of the oxygen-limited myocardium.[1,2] There is strong support for this hypothesis in both rat[3,4] and dog hearts[5] provided that anoxia is accompanied by maintenance of coronary flow rate. But in severe ischemia the accumulation of the eventual end products of anaerobic glycolysis, lactate and hydrogen ion, appears to limit the increase in the rate of glycolytic flux both in rat[6] and in dog hearts[7] and the arguments for the use of glucose-insulin-potassium might seem less strong. Nevertheless, studies from this laboratory[8] have shown that infusions of glucose-insulin-potassium were able to increase cardiac glycogen and tissue potassium ion/sodium ion ratios in the baboon heart within the 1st hour of myocardial infarction. Two questions were posed by those studies. First, could the effect of glucose-insulin-potassium be related to altered myocardial extraction of glucose[2] or of free fatty acids?[9] Second, would these early metabolic changes be reflected in evidence of lessened tissue necrosis if glucose-insulin-potassium infusions were given for longer periods? Early pathologic signs of myocardial infarction 6 hours after coronary ligation can be correlated with the degree of depletion of glycogen or decrease in the K^+/Na^+ ratio.[10] Epicardial S-T segment ele-

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vation is another index of necrosis that may have clinical application in the form of precordial mapping,[11,12] but the development of frequent ectopic beats more than 6 to 8 hours after ligation in the dog makes it difficult to follow electrocardiographic changes.

In the present study a glucose-insulin-potassium solution was infused for 6 hours, starting 30 minutes after ligation, with the aim of testing effects on myocardial substrate metabolism, tissue glycogen, K^+/Na^+ ratio and epicardial S-T segment elevation. Effects on myocardial substrate metabolism were monitored by measurements of arteriovenous differences of glucose, free fatty acid, lactate and oxygen across the whole heart.

The data suggest that glucose-insulin-potassium acts beneficially on indexes of necrosis in this model in part by increasing glucose and decreasing free fatty acid extraction by the heart, and that measurements of arteriovenous differences and precordial S-T segment changes could help to evaluate the effects of a glucose-insulin-potassium solution in clinical situations.

Methods

Animals: Thirty mongrel dogs of either sex, weighing 15 to 31 kg, were anesthetized by a single intravenous injection of sodium pentobarbital (30 mg/kg) body weight, intubated and respired at 12.5 ml/kg and 24 respirations/min with room air by a Harvard respirator. Anesthesia was maintained with use of intermittently administered phenobarbitone. The preligation arterial pH was 7.33 ± 0.01; arterial partial pressure of oxygen was 86 ± 3 mm Hg, and of carbon dioxide was 28 ± 3 mm Hg (mean values ± standard error of the mean, no. = 18 for each).

Operative procedure: After cannulation of the femoral artery and vein and attachment of limb leads for electrocardiographic recording, the chest was opened by a lateral thoracotomy, the heart suspended in a pericardial cradle and a coronary sinus catheter inserted from a leg vein. The left anterior descending coronary artery was ligated just above the junction of the terminal and apical branches, thereby producing a standard infarction.[13] If a large branch of the posterior interventricular artery supplied the zone of the expected apical infarction, it was also ligated (Fig. 1). Approximately 1 1/2 hours after ligation the chest was closed in layers with an indwelling drainage tube and the dog was allowed to breathe on its own.

Electrocardiographic procedures: Limb leads were recorded by a two-channel Corbin-Farnsworth machine. Precordial leads were taken with a hand-held wire electrode, recorded on the V channel of the recorder; patterns of S-T change were similar to those obtained with a wick electrode.[14] Epicardial recordings were randomly taken from numerous sites situated throughout the ischemic zone and adjacent tissue on the anterior exposed surface of the heart. While one person placed the epicardial electrode, another read off the degree of S-T change from the recording paper, and the values were noted on a hand-drawn map of the heart (Fig. 2). Recordings were made (1) before ligation, to eliminate hearts damaged by the dissection procedure; (2) 15 to 30 minutes after ligation (Fig. 2A), and (3) 6 hours after ligation (Fig. 2B).

Infusions: In eight dogs, 30 minutes after ligation, an infusion of glucose-insulin-potassium solution (50 percent dextrose, 50 units of insulin, 50 mEq/liter of potassium) into the femoral vein was given at the rate of 0.1 ml/kg per min until the time of biopsy of the heart. Seven dogs were given no infusion of any kind.

Control dogs: In eight dogs, the heart was suspended in a pericardial cradle but the coronary artery was not dissected and biopsies were performed approximately at the time that arterial ligation would have been done (0 time control). In another seven dogs, the artery was also not dissected but the chest closed and the experiment continued as for ligated dogs not given glucose-insulin-potassium (6 hour control).

Biochemical analyses: Arterial and coronary sinus blood gases, sodium and potassium were monitored every 30 to 60 minutes by the Astrup technique and with an IL flame photometer. Samples for blood glucose (usually in triplicate), free fatty acids and lactate were also taken at the same time intervals. Analytic details are given elsewhere.[8] Arterial plasma proteins, albumin and urea were measured with an automated 12 channel Technicon procedure. Procedures for calculating the arterial oxygen content and oxidation extraction ratio were as before.[15]

Biopsies: Six hours after ligation the chest was reopened. After the epicardial electrocardiogram had been recorded, 5 drill biopsy specimens were taken (6 1/2 hours after ligation) in rapid succession for analysis of high energy phosphate compounds and for lactate. The dental drill technique of Pool et al.[16] was modified to give a core of tissue 3 mm in diameter that was immediately expelled by positive pressure into liquid nitrogen (freon was initially used but similar values were obtained with liquid nitrogen).

The heart was then excised by aortic transection, arrested in ice-cold 0.25 M sucrose, and further biopsy specimens were taken for glycogen, K^+/Na^+ and histologic studies. Samples

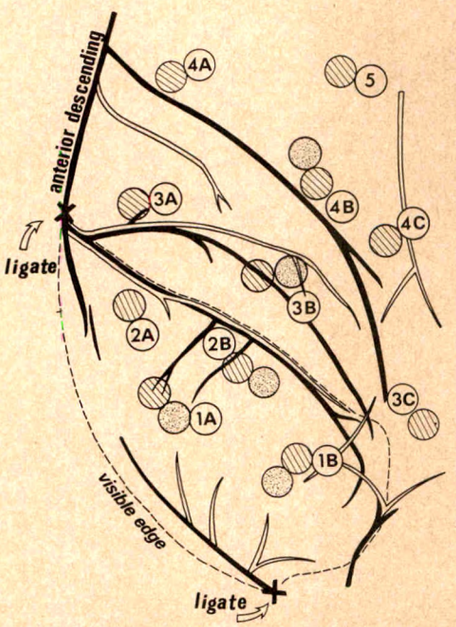

FIGURE 1. Biopsy sites in relation to map of anterior surface of heart. Arteries **(solid black)** and veins **(white)** are shown in relation to sites of ligation, the early visible edge of the infarction, and biopsy sites 6 1/2 hours after ligation. Glycogen sites are **cross-hatched,** K^+/Na^+ sites indicated by **numbers** and high energy phosphate sites **stippled.** In this dog, the left anterior descending coronary artery was relatively small, and the terminal branch of the posterior interventricular artery had also been ligated **(lower arrow)** to produce a standard apical infarct.[13] Biopsy specimens were taken from the anatomic inner infarct zone 1, the peripheral infarct zone 2, the periinfarct zone 3 and the nonischemic zone 4. For further description of these zones, see text.

for glycogen were frozen in liquid N_2, but those for K^+/Na^+ ratios were ejected directly into the extraction medium. Samples for histologic studies, taken with a drill 1 mm in diameter, were ejected into 5 percent buffered formaldehyde. Four to five biopsy specimens were usually taken from the area of infarction for each variable analyzed, two from the center zone and two or three from the periphery. Three samples were taken from the apparently normal bordering tissue and a further four from tissue far away from the infarction (Fig. 1). Thus about 12 biopsy specimens were taken from each heart for each variable, making a total of 24 biochemical biopsy specimens plus 5 histologic biopsy specimens taken after cardiac arrest, in addition to the 5 biochemical biopsy specimens previously taken from the beating heart for analysis of high energy phosphate compounds (Fig. 3).

Delineation of infarcting tissue: A dark blue area formed in the territory bounded by the terminal and apical branches of the left anterior descending artery and extending to just beyond the apical branch (viewing the heart from the apex). This initial visible edge (Fig. 1) was not defined clearly when the chest was reopened and was, therfore, the "early" visible edge, which corresponded fairly well with the early electrocardiographic edge. The latter was delineated by multiple epicardial recordings and by epicardial "sweeps," where S-T elevation over the dark area changed to an isoelectric or occasionally depressed S-T segment as the electrode left the blue area and moved into normal tissue.[14] The hand-held wire electrode allowed good definition of the electrocardiographic edge.

The periinfarct border zone was the zone lying between the visible edge of the zone of infarction and the next proximal anterolateral branch of the left anterior descending coronary artery (Fig. 1). The nonischemic zone was that tissue lying toward the base of the heart above the periinfarct zone. All zones were weighed at the end of each experiment.

Processing of biopsy specimens: Biopsy specimens for analysis of adenosine triphosphate and related compounds were kept frozen overnight in liquid N_2 and then split in half on an aluminium block chilled in liquid N_2. Each half (approximately 80 mg) was weighed on a prechilled pan and deproteinized and analyzed for adenosine triphosphate, creatine phosphate, adenosine diphosphate, adenosine monophosphate, inorganic phosphate and lactate by methods previously described.[8] When adenosine diphosphate and adenosine monophosphate were analyzed, endocardial and epicardial samples were pooled.

Biopsy specimens for glycogen were also split into endocardial and epicardial halves, weighed, digested in potassium

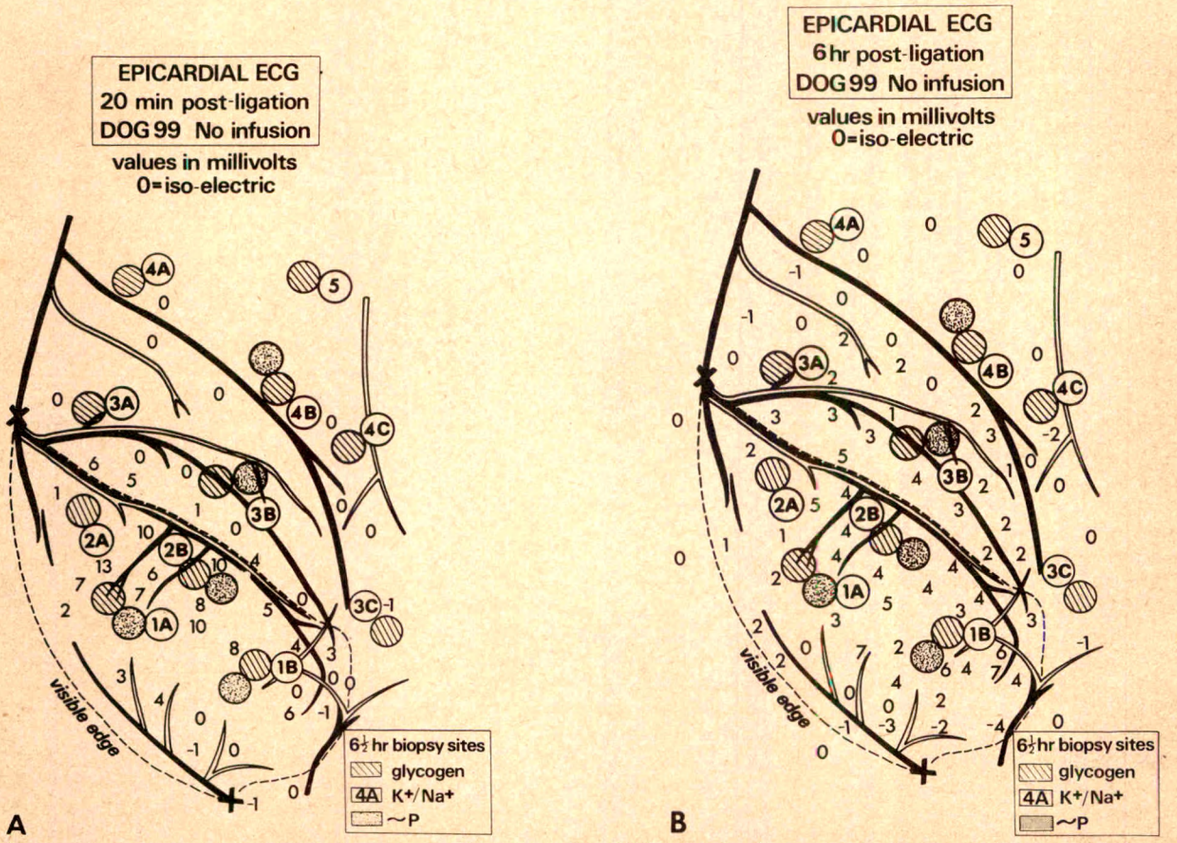

FIGURE 2. Dog 99. Example of epicardial electrocardiographic changes after ligation showing degree of S-T elevation in millivolts in relation to final biopsy sites. **A,** 20 minutes after ligation. In this experiment, 23 recordings were taken from the infarct (zones 1 and 2), which is shown separated by a **stippled line** indicating the early visible edge. There are 11 recordings from zone 3 and nonischemic zone 4. The two values in the periinfarct zone near the inferior ligation have been ignored. Mean values ± standard error of the mean are 4.6 ± 0.9 mv in the infarct zone, 1.3 ± 0.7 in the periinfarct zone and 0 in the nonischemic zone. Note the marked site to site variation in degree of S-T elevation. **B,** 6 hours after ligation. In this experiment mean elevation is 2.6 ± 0.5 mv (no. = 34) in the infarct zone, 2.2 ± 0.7 (no. = 25) in the periinfarct zone and 0.1 ± 0.5 (no. = 8) in the nonischemic zone. Note the increasing number of sites with S-T elevation in the periinfarct zone in this heart not infused with glucose-insulin-potassium. ~P = high energy phosphate; symbols as in Figure 1.

hydroxide, glycogen-precipitated and assayed as glucose by the glucose 6-phosphate dehydrogenase method.

Biopsies for K^+/Na^+ ratios were first frozen in liquid N_2, then split into epicardial and endocardial parts, digested in nitric acid, dried, weighed, redigested and assayed by an IL flame photometer. The approximate size of the visible infarct was measured as before.[8]

Biopsy specimens for histologic examination were cut in the routine manner after fixation, and stained by hematoxylin-eosin, periodic acid-Schiff with or without diastase digestion, Best's carmine, and hematoxylin basic fuchsin picric acid. Seven criteria of infarction were searched for: edema, congestion, waviness of myofibers, myofibrillar degeneration, polymorphonuclear infiltration, glycogen depletion and fuchsinophilia and fuchsinorrhagia. A scoring was used classifying each biopsy specimen on a scale of 0 (normality) to 3+ (severe abnormality). A total score of 5 or more correlated well with the anatomically defined infarct zone. Details are given elsewhere.[10]

Assessment of extent of ischemic damage: The extent of ischemic damage was assessed by the degree of K^+/Na^+ depletion[10,17] and the degree of glycogen depletion[18] using methods similar to those of Jennings et al.[19] for relating infarction to K^+ loss. The weight of each infarct zone had to be known for this calculation. Thus a lesion in which area 1 had only 20 percent of the normal K^+/Na^+ value was regarded as having 80 percent ischemic damage. The sum of K^+/Na^+ depletions in zones 1, 2 and 3 was taken together as the extent of ischemic damage. Similar calculations were made for glycogen depletion, which is closely linked to histologic evidence of necrosis.[10,18]

Tests of statistical significance: Mean values ± standard error of the mean and P values from Student's t test were computed by standard procedures. P values greater than 0.05 were held to be not significant (NS).

Results

Arteriovenous differences across the heart and oxygen extraction ratios (Tables I to IV): Preligation values represent data from animals without infusion, each animal being represented by the mean of values 1 1/2 hours before ligation. Postligation samples were also grouped and values in animals without infusion compared with values in animals with infusion. Glucose-insulin-potassium infusion increased the blood glucose nearly threefold (from 4.3 to 11.5 millimolar) and there was also a threefold increase in the arteriovenous differences of glucose. The oxygen extraction ratio of glucose also increased about three times from 26 to 73 percent (that is, in infused dogs, glucose could account—if fully oxidized—for 73 percent of the oxygen taken up at that time).

Basal blood lactate values were about four times higher than in previous experiments in greyhound dogs; variable blood lactate values in dogs have already been commented on.[20] The arteriovenous differences for lactate were also about three times larger, and lactate oxidation could account for approximately 50 percent of the oxygen taken up and was the major fuel of the heart in dogs without infusion. Postligation arterial blood lactate values were higher in the group given glucose-insulin-potassium (Table I), but arteriovenous differences and oxygen extraction ratio values were similar in the groups with and without infusion.

Free fatty acid levels were relatively low throughout the study; the preligation value was approximately 425 μEq/liter compared with about 700 μEq/liter in previous experiments.[15] High circulating lactate values are known to decrease circulating free fatty acid values and myocardial extraction of free fatty acid.[21] Arteriovenous differences and oxygen extraction ratio of free fatty acids were also lower in the present experiments. In dogs given glucose-insulin-potassium, circulating free fatty acid values were very low, the arteriovenous difference was small, and the oxygen extraction ratio was suppressed to only 6 percent. The free fatty acid/albumin molar ratio[7] fell from 2.19 in the group without infusion to 1.06 in the group with infusion (Table IV).

Values for total oxygen extraction ratio have a large standard error and must be viewed with some reserve. However, postligation oxygen extraction ratio values for dogs given glucose-insulin-potassium were higher than in the group without infusion, compatible with a nonoxidative fate of glucose such as glycogen storage or lipid formation.

The arterial K^+ value did not rise with glucose-insulin-potassium infusion, indicating either uptake of K^+ by tissue

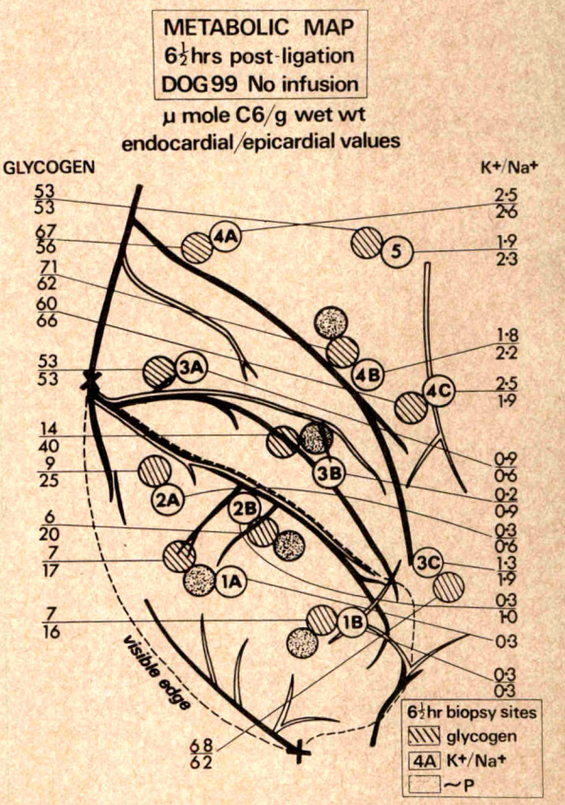

FIGURE 3. Dog 99. Values for tissue glycogen and K^+/Na^+ ratios in various biopsy sites 6 1/2 hours after ligation. Note the greater decrease in glycogen values in endocardial (numerators) than in epicardial (denominators) biopsy sites in the infarct zones. Endocardial K^+/Na^+ values are also generally lower than epicardial values. The decreased glycogen adjacent to biopsy site 3B corresponds with the 6 hour value for epicardial S-T elevation at that site, whereas normal glycogen values near sites 3A and 3C correspond with relatively normal S-T values at those sites (Fig. 2B). K^+/Na^+ values are also decreased near site 3B, but normal glycogen values near sites 3A and 3C contrast with K^+/Na^+ depression, indicating that there may be considerable metabolic variation even in adjacent biopsy sites. ~P = high energy phosphate and lactate biopsy sites with the following values (endocardial/epicardial): Adenosine triphosphate (μmole/g): site 1A 2.9/1.4; site 1B 0.2/1.8; site 2B 0.0/0.9; site 3B 0.2/3.3; site 4B 5.2/5.4. Creatine phosphate (μmole/g): site 1A 6.6/6.6; site 1B 2.0/8.5; site 2B 1.2/3.0; site 3B 1.1/11.0; site 4B 9.7/12.3. Inorganic phosphate (μmole/g): site 1A 8.5/8.9; site 1B 8.0/9.2; site 2B 8.0/6.1; site 3B 7.7/3.5; site 4B 4.5/2.0. Lactate (μmole/g): site 1A 4.9/7.5; site 1B 14.0/7.3; site 2B 11.6/3.9; site 3B 11.3/2.6; site 4B 2.0/1.5. Symbols as in Figure 1.

TABLE I

Effect of Coronary Ligation and of Infusion of Glucose-Insulin-Potassium on Arterial Concentrations and Arteriovenous Differences of Glucose, Lactate, Free Fatty Acid and Potassium

	Before Ligation	P	After Ligation		
			Without Infusion	P	With Infusion
Glucose (mM)					
Arterial concn.	4.86 ± 0.21 (19)	NS	4.34 ± 0.12 (52)	$<10^{-9}$	11.45 ± 0.80 (61)
a-v difference	0.28 ± 0.07 (19)	NS	0.20 ± 0.03 (52)	<0.004	0.59 ± 0.12 (59)
Lactate (mM)					
Arterial concn.	2.92 ± 0.34 (17)	<0.03	2.20 ± 0.14 (62)	<0.0006	3.11 ± 0.23 (42)
a-v difference	0.90 ± 0.11 (17)	NS	0.69 ± 0.07 (62)	NS	0.65 ± 0.09 (42)
Free fatty acids (mM)					
Arterial concn.	0.425 ± 0.057 (14)	NS	0.436 ± 0.035 (42)	$<10^{-9}$	0.160 ± 0.014 (42)
a-v difference	0.116 ± 0.020 (13)	NS	0.109 ± 0.017 (42)	<0.00002	0.021 ± 0.008 (41)
Potassium (mEq/liter)					
Arterial concn.	4.5 ± 0.02 (14)	NS	4.2 ± 0.1 (42)	NS	4.4 ± 0.1 (41)
a-v difference	−0.02 ± 0.05 (14)	NS	−0.03 ± 0.04 (42)	NS	−0.03 ± 0.05 (41)

Values expressed as mean values ± standard error of the mean with number of samples in parentheses. Values before ligation were obtained 1.5 hours before ligation in all animals; values after ligation represent hourly samples obtained 1 to 6 hours after ligation.
a-v = arteriovenous; concn. = concentration; NS = not significant; *P* = probability.

or urinary loss. The arteriovenous difference of K^+ across the heart was slightly negative in all groups, suggesting that infused K^+ was taken up by noncardiac tissue, but the methods were not sensitive enough to measure small degrees of K^+ uptake in the heart.

Other circulatory changes (comparing groups without infusion and groups with infusion after ligation) were a decreased hemoglobin level, a decreased calculated O_2 content of the blood and a decreased arteriovenous difference of O_2 (Table III). Coronary ligation caused a reduction in plasma proteins and plasma albumin in dogs with and without infusion, but no differences were apparent between the latter groups.

Epicardial electrocardiographic changes as result of glucose-insulin-potassium (Table V): In the infarct zones, the mean epicardial S-T segment elevation decreased from 10.6 to 6.4 mv in dogs without infusion, and to 3.4 mv in dogs given glucose-insulin-potassium. In the periinfarct border zone, S-T elevation nearly doubled in dogs without infusion, but did not increase in those with infusion. In the "nonischemic" zone 4 there was again a small increase in S-T segment elevation in dogs without infusion (from −0.1 to 0.8 mv) but no such increase in dogs given glucose-insulin-potassium. Thus infusion of glucose-insulin-potassium accelerated the rate of fall of the epicardial S-T segment in the infarct zones and prevented the development of a small degree of S-T elevation in the periinfarct and nonischemic zones.

Tissue metabolic changes: The effects of glucose-insulin-potassium infusion on tissue metabolic values are shown in Tables VI to VIII. The major effects were in the periinfarct border zone, where the K^+/Na^+ ratio rose, K^+ increased, Na^+ decreased, glycogen increased, inorganic phosphate decreased and there were rises in the phosphate potential ratios, here measured by (adenosine triphosphate + creatine phosphate)/(inorganic phosphate) and (adenosine triphosphate)-/(adenosine diphosphate + inorganic phosphate). Other changes included: (1) an increased endocardial adenosine triphosphate value in the infarct area; (2) a decreased inorganic phosphate value in the endocardial infarct zone and in the nonischemic zone; (3) an increased lactate value in the central infarct and nonischemic areas; and (4) a decreased adenosine diphosphate and adenosine monophosphate value in the nonischemic zone.

Effect of ligation on nonischemic tissue: Nonischemic tissue from animals with coronary arterial ligation was compared with tissue from hearts taken directly after opening the chest (0 time control group) or from the control group maintained for 6 1/2 hours without coronary ligation. Values of adenosine triphosphate, creatine phosphate, inorganic phosphate, lactate, K^+, Na^+ and K^+/Na^+ and dry/wet weight ratios did not differ between the nonischemic zones of infarcted hearts and hearts in the 6 1/2 hour nonligated control group, except that glycogen rose in the nonischemic zone of the former, in keeping with histochemical observations in infarcted human hearts.[22] These conclusions are based on at least three biopsy specimens from each zone in seven dogs, with division into endocardial and epicardial values (that is, 42 or more biopsy specimens per zone). Values for adenosine triphosphate, creatine phosphate, inorganic phosphate, lactate, adenosine diphosphate and adenosine monophosphate in hearts in the 0 time control group were similar to values in the 6 1/2 hour control group and in the nonischemic zone of noninfused ligated hearts. None of the control values showed any major regional difference from apex to base of the heart.

Heart rhythm: By the end of 6 hours, the majority of animals manifested frequent ectopic beats, but usually sufficient beats were sinus in origin to allow assessment of S-T segment development.

TABLE II

Effect of Coronary Ligation and Infusion of Glucose-Insulin-Potassium on Oxygen Extraction Ratios of Glucose, Lactate and Free Fatty Acids (FFA)

Oxygen Extraction Ratios (%)	Before Ligation	P	After Ligation		
			Without Infusion	P	With Infusion
Glucose	26 ± 4 (19)	NS	23 ± 3 (52)	0.001	73 ± 14 (59)
Lactate	50 ± 6 (17)	NS	36 ± 4 (62)	NS	39 ± 5 (42)
FFA	27 ± 4 (13)	NS	21 ± 3 (42)	0.0007	6 ± 3 (41)
Total	101 ± 8 (13)	NS	80 ± 6 (42)	0.02	118 ± 15 (41)

Values expressed as mean ± standard error of the mean with number of samples in parentheses.
For calculation of oxygen extraction ratios see Ref 15. No allowance has been made for the "oxygen-wasting" theoretically possible during FFA-metabolism (see text).
NS = not significant; *P* = probability.

Extent of ischemic damage: *a. Anatomic definition of early limits of infarct.* After all the biopsy specimens had been taken, the early visible edge, as drawn on a map of the heart and localized by the epicardial vessels (Fig. 1), was cut out to separate the infarct and periinfarct zones; the latter zone was then separated from the nonischemic zone, and each zone was weighed. The average initial infarct weight, estimated in this way, was about 12 percent of the whole heart in each group (about one third being area 1 and two thirds area 2). The periinfarct zone weighed about 7 percent of the whole heart.

b. Biochemical definition. Using the degree of depression of the K^+/Na^+ ratio as an index of ischemic damage, the final depression of the K^+/Na^+ ratio was 12.7 percent in the group without infusion and 9.5 percent in the group with infusion. If one uses the degree of glycogen depletion as an index of ischemic damage, the total cardiac glycogen level fell by 10.3 percent in dogs without infusion and by 7.8 percent in dogs given glucose-insulin-potassium. These approximations suggest that glucose-insulin-potassium decreased biochemical damage by 20 to 25 percent. If one considers only the infarct and periinfarct zones, glucose-insulin-potassium decreased the extent of glycogen depletion by 28 percent. The degree of depletion of tissue creatine phosphokinase was not helpful in assessing infarct size in these experiments because major loss of tissue creatine phosphokinase takes place only later. However, Maroko et al.[11] have related the degree of S-T elevation 15 minutes after ligation to creatine phosphokinase depletion at 24 hours; hence it may be expected that an accelerated fall of epicardial S-T elevation in the infarct zone

TABLE III

Blood PO_2, Hemoglobin and Calculated O_2 Content Before and After Coronary Ligation

			After Ligation		
	Before Ligation	*P*	Without Infusion	*P*	With Infusion
Hemoglobin (g/100 ml)	16.9 ± 0.4 (14)	NS	16.7 ± 0.4 (47)	$<10^{-4}$	14.1 ± 0.3 (25)
Calculated O_2 content (ml/100 ml)	22.5 ± 0.09 (20)	NS	21.5 ± 0.18 (37)	$<10^{-9}$	18.6 ± 0.16 (45)
Calculated a-v O_2 difference (ml/100 ml)	12.2 ± 0.4 (17)	<0.02	13.8 ± 0.4 (34)	$<10^{-6}$	11.1 ± 0.3† (45)

Values expressed as mean ± standard error of the mean with number of samples in parentheses.
*Conversion factor: hemoglobin = hematocrit × 2.84 ± 0.03 (no. = 49); the O_2 content of hemoglobin is taken as 1.38 ml/g (see Ref 51).
†*P* <0.05 versus values in group before ligation.
a-v = arteriovenous; NS = not significant; *P* = probability.

TABLE IV

Plasma Proteins and Albumin and FFA/Albumin Molar Ratios in Arterial Blood Before and After Coronary Ligation

			After Ligation		
	Before Ligation	*P*	Without Infusion	*P*	With Infusion
Plasma proteins (g/100 ml)	6.7 ± 0.1 (9)	<0.003	5.6 ± 0.2 (14)	NS	5.2 ± 0.2 (16)
Plasma albumin (g/100 ml)	1.7 ± 0.08 (9)	<0.001	1.3 ± 0.07 (14)	NS	1.1 ± 0.04 (16)
Blood urea (mg/100 ml)	39 ± 3 (9)	NS	34 ± 2 (14)	<0.008	26 ± 2 (16)
FFA/albumin (molar ratio)	1.62 ± 0.30 (7)	NS	2.19 ± 0.35 (14)	<0.007	1.06 ± 0.06 (12)

Values expressed as mean ± standard error of the mean with number of samples in parentheses.
FFA = free fatty acid; NS = not significant; *P* = probability.

TABLE V

Effect of Glucose-Insulin-Potassium Infusions of 6 Hours' Duration on Epicardial S-T Elevation After Coronary Ligation

			Final Postligation Reading† (mv)		
	Early Postligation Reading* (mv)	*P*	Without Infusion	*P*	With Infusion
Infarct zone	10.6 ± 1.2 (367)	<0.02	6.4 ± 0.6 (213)	<0.00003	3.4 ± 0.4 (234)
Periinfarct border zone	1.0 ± 0.3 (97)	<0.001	2.2 ± 0.2 (77)	<0.02	1.5 ± 0.2 (54)
Nonischemic zone	−0.1 ± 0.1 (50)	<0.01	0.8 ± 0.3 (47)	<0.01	−0.3 ± 0.2 (33)

Values expressed as mean ± standard error of the mean for the number of observations in parentheses (sum of all values of all sites for each zone from all hearts in group, see Fig. 1)
*Taken 15 to 30 minutes after coronary arterial ligation and before start of infusion period (Fig. 1).
†Taken after 6 hours of glucose-insulin-potassium infusion or after similar control period (Fig. 2A).
P = probability.

would have been associated with decreased tissue necrosis at 24 hours. At 6 1/2 hours after ligation, histologic improvement in dogs given glucose-insulin-potassium was evident only in the periinfarct zone where the average histologic score fell from 7.8 to 3.2 ($P < 0.005$).[10]

Assessment of model: An important defect of our model, and possibly of other models using mongrel dogs, is that there were relatively low circulating values of free fatty acid, hypoalbumineamia and high circulating values of lactate. All of these were absent in our previous studies in greyhounds,[15] presumably because the latter were in much better nutritional state and in excellent general health. These limitations require that data on mongrel dogs be evaluated together with data on other infarct models such as the isolated perfused rat heart,[23] where better control of circulating substrate and albumin concentrations is possible.

Discussion

Effects of glucose-insulin-potassium on substrate metabolism: These studies confirm previous reports of a beneficial effect of glucose, insulin and potassium on developing myocardial infarction in the dog and baboon.[8,11,24,25] but these appear to be the first experiments in which tissue metabolic values are assessed in the light of arteriovenous substrate differences.

The combined total for the oxidation extraction ratio for glucose, lactate and free fatty acid in dogs given glucose-insulin-potassium infusions exceeded 100 percent, a finding compatible with nonoxidative fates of glucose. One such fate would be glycogen formation in keeping with increased tissue glycogen values. Another fate of the glucose extracted could be increased provision of alpha-glycerophosphate for intracellular esterification of tissue free fatty acid. In the absence of measurements of tissue neutral lipids, it is not possible to check whether the excess glucose oxygen extraction ratio could precisely be accounted for as glycogen and lipid formation, but the latter fate also seems likely.[26] Another possibility is that some of the glucose uptake formed lactate, thereby accounting for the unchanged lactate arteriovenous differences in spite of increased arterial lactate in dogs given glucose-insulin-potassium infusions. Normally, an increased circulating lactate value should be accompanied by increased lactate extraction.[9,27] Because arteriovenous differences were relatively small in relation to the circulating glucose concentrations, technical problems arose in spite of triplicate glucose assays. Nevertheless, an effect of glucose-insulin-potassium in increasing the myocardial glucose extraction is in agreement with data in patients with stable coronary heart disease.[9]

The arterial free fatty acid values were lower than those found in patients within the early hours of myocardial infarction.[28] However, the albumin values were also low in these dogs (preligation value 1.7 g/100 ml). Hence, the preligation free fatty acid/albumin molar ratio was about 1.6, whereas after ligation the ratio was about 2.2 in dogs without infusion and 1.1 in those with infusion. In patients with acute infarction the ratio is about 1.5.[29] Since there is evidence that the free fatty acid/albumin molar ratio may be responsible for the rate

TABLE VI

Effects of Glucose-Insulin-Potassium (GIK) Infusion of 6 Hours' Duration on Tissue Metabolic Changes in Infarcting Dog Heart

	Central Infarct (Zone 1)	Peripheral Infarct (Zone 2)	Periinfarct (Zone 3)	Nonischemic (Zone 4)
Glycogen				
Control (6 hr)	39.5 ± 1.7 (43)	41.9 ± 1.7 (46)	37.8 ± 1.3 (45)	39.3 ± 1.6 (42)*
No GIK	8.4 ± 1.9 (16)	11.2 ± 1.6 (36)	44.7 ± 2.6 (48)	54.0 ± 1.7 (51)*
GIK	15.1 ± 2.5 (22)	20.3 ± 2.3 (48)	59.4 ± 2.7 (48)	64.0 ± 2.0 (38)
P	= 0.05	<0.004	<0.0002	<0.0003
K^+				
Control (6 hr)	71.5 ± 1.0 (31)	71.0 ± 1.5 (29)	72.8 ± 1.0 (31)	74.4 ± 0.9 (32)
No GIK	43.8 ± 2.7 (15)	46.0 ± 2.2 (34)	68.9 ± 2.2 (47)	77.3 ± 1.3 (43)
GIK	50.9 ± 4.3 (22)	50.8 ± 2.4 (43)	76.2 ± 1.7 (42)	77.4 ± 1.2 (55)
P	NS	NS	<0.02	NS
Na^+				
Control (6 hr)	40.0 ± 1.8 (31)	36.8 ± 2.3 (29)	34.9 ± 1.1 (31)	34.1 ± 0.7 (29)
No GIK	127.1 ± 10.3 (50)	103.5 ± 5.7 (32)	61.3 ± 4.6 (50)	35.7 ± 1.3 (43)
GIK	113.0 ± 8.8 (24)	110.8 ± 5.3 (46)	46.0 ± 2.6 (41)	37.0 ± 1.0 (53)
P	NS	NS	<0.008	NS
K^+/Na^+				
Control (6 hr)	1.95 ± 0.06 (37)	2.09 ± 0.06 (35)	2.12 ± 0.07 (39)	2.18 ± 0.05 (38)
No GIK	0.44 ± 0.05 (16)	0.48 ± 0.03 (49)	1.43 ± 0.09 (50)	2.27 ± 0.05 (43)
GIK	0.64 ± 0.11 (22)	0.56 ± 0.05 (46)	1.87 ± 0.09 (41)	2.17 ± 0.06 (53)
P	NS	NS	<0.001	NS
Dry/wet weight ratio				
Control (6 hr)	20.5 ± 0.1 (44)	20.8 ± 0.2 (39)	21.1 ± 0.1 (43)	20.8 ± 0.2 (48)
No GIK	16.9 ± 0.7 (16)	16.9 ± 0.3 (50)	19.3 ± 0.4 (49)	20.6 ± 0.2 (44)
GIK	15.8 ± 0.6 (24)	16.0 ± 0.4 (47)	19.6 ± 0.3 (46)	19.9 ± 0.2 (56)
P	NS	NS	NS	NS

* = $P < 0.05$.

Values expressed as mean values ± standard error of the mean for number of samples in parentheses. For explanation of biopsy zones see Figure 1. Units: glycogen, μmole C6/g wet weight; K^+ and Na^+, mEq/kg fresh weight; dry/wet weight ratio as percent. *P* values indicate difference between dogs without and with glucose-insulin-potassium infusion.

NS = not significant.

of free fatty acid uptake by the heart and may help to determine the "toxic" effects of free fatty acid,[7,30] the decrease of the ratio from 2.2 to 1.1 by glucose-insulin-potassium may be significant. In the isolated rat heart with coronary ligation, glucose or insulin, or both, lowers the rate of release of lactate dehydrogenase compared with free fatty acid perfusates, and a high free fatty acid/albumin molar ratio accelerates the release of lactate dehydrogenase.[23]

Arteriovenous differences were measured across the whole heart but not across the ischemic zone, which differs greatly in its regional metabolism.[31] However, present evidence is that glucose-free fatty acid interaction takes place in ischemic tissue much as in normal tissue, probably because patterns of oxidative metabolism persist in the ischemic tissue until the level of blood flow is extremely low.[26]

Effects of glucose-insulin-potassium on arteriovenous difference of oxygen across the heart: After coronary arterial ligation, myocardial oxygen extraction (arteriovenous difference) increased (Table III), probably to compensate in part for the regional decrease in blood flow. With infusion of glucose-insulin-potassium, the arteriovenous O_2 difference fell rather than rose. Stanley et al.[9] attributed a similar decrease in O_2 extraction in patients with stable coronary artery disease to decreased free fatty acid extraction because it appeared unlikely that there was decreased myocardial contractility during glucose-insulin-potassium infusion. Our data also show a positive correlation between decreased O_2 and decreased free fatty acid extraction. However, another relation between the decreased O_2 extraction and the decreased arterial O_2 content is associated with a decreased he-

TABLE VII

Effect of Infusions of Glucose-Insulin-Potassium (GIK) of 6 Hours' Duration on Myocardial Energy Metabolism in Infarcting Dog Heart (μmole/g wet weight)

	Central Infarct (Zone 1)	Peripheral Infarct (Zone 2)	Periinfarct Border (Zone 3)	Nonischemic (Zone 4)
ATP				
Control (6 hr)	4.57 ± 0.32 (17)	4.79 ± 0.14 (17)	4.63 ± 0.25 (15)	4.91 ± 0.20 (27)
No GIK	0.81 ± 0.22 (24)**	0.91 ± 0.40 (10)**	2.47 ± 0.41 (17)**	5.01 ± 0.18 (20)
GIK	0.89 ± 0.22 (24)††	1.60 ± 0.30 (10)††	3.38 ± 0.49 (15)†	5.01 ± 0.29 (20)
P	NS	NS	NS	NS
CP				
Control (6 hr)	9.45 ± 0.52 (18)	10.16 ± 0.53 (17)	10.13 ± 0.68 (15)	10.05 ± 0.38 (21)
No GIK	1.94 ± 0.44 (26)**	1.08 ± 0.34 (10)**	5.83 ± 0.88 (19)*	11.28 ± 0.28 (20)
GIK	1.27 ± 0.27 (24)††	3.91 ± 1.15 (10)††	8.25 ± 1.03 (15)	11.10 ± 0.55 (20)
P	NS	0.03	NS	NS
ADP				
Control (1 hr)	0.850 ± 0.049 (5)	0.779 ± 0.055 (5)	0.901 ± 0.048 (5)	0.775 ± 0.044 (5)
No GIK	0.381 ± 0.036 (14)**	0.332 ± 0.082 (6)**	0.460 ± 0.071 (8)**	0.803 ± 0.039 (10)
GIK	0.324 ± 0.049 (14)††	0.365 ± 0.040 (7)††	0.595 ± 0.055 (7)††	0.581 ± 0.068 (11)
P	NS	NS	NS	<0.0125
AMP				
Control (1 hr)	0.090 ± 0.025 (5)	0.101 ± 0.033 (5)	0.105 ± 0.020 (4)	0.096 ± 0.030 (5)
No GIK	0.112 ± 0.019 (15)	0.079 ± 0.007 (9)	0.055 ± 0.008 (6)*	0.065 ± 0.007 (10)
GIK	0.085 ± 0.013 (15)	0.060 ± 0.019 (8)	0.037 ± 0.009 (7)††	0.038 ± 0.010 (11)††
P	NS	NS	NS	<0.05
Pi				
Control (6 hr)	2.92 ± 0.23 (15)	3.10 ± 0.32 (13)	3.04 ± 0.27 (13)	3.11 ± 0.21 (23)
No GIK	11.22 ± 0.94 (22)**	9.32 ± 1.30 (10)**	6.38 ± 0.95 (15)**	3.31 ± 0.30 (16)
GIK	9.51 ± 0.94 (25)††	6.66 ± 0.95 (11)††	3.29 ± 0.38 (16)	2.40 ± 0.29 (21)
P	NS	NS	<0.005	<0.04
Lactate				
Control (6 hr)	2.07 ± 0.22 (16)	2.36 ± 0.37 (18)	2.29 ± 0.46 (16)	2.20 ± 0.36 (19)
No GIK	15.74 ± 1.94 (26)**	13.21 ± 2.32 (8)**	5.80 ± 1.33 (14)*	2.50 ± 0.37 (18)
GIK	23.29 ± 1.67 (27)††	14.17 ± 2.25 (13)††	6.68 ± 1.05 (13)††	4.60 ± 0.61 (21)††
P	<0.005	NS	NS	<0.01
(ATP + CP)/Pi				
Control (1 hr)	4.82 ± 0.60 (8)	5.31 ± 0.52 (9)	5.81 ± 0.54 (9)	6.16 ± 0.31 (16)
No GIK	0.33 ± 0.09 (19)**	0.25 ± 0.09 (10)**	2.05 ± 0.40 (15)**	5.47 ± 0.46 (16)
GIK	0.35 ± 0.13 (11)††	1.61 ± 0.70 (10)††	6.04 ± 1.75 (15)	8.51 ± 0.92 (20)†
P	NS	NS	<0.04	<0.01
ATP/(ADP + Pi)				
Control (1 hr)	1.25 ± 0.26 (3)	1.24 ± 0.19 (3)	1.40 ± 0.06 (3)	1.52 ± 0.06 (6)
No GIK	0.14 ± 0.042 (22)**	0.11 ± 0.05 (10)**	0.45 ± 0.10 (15)**	1.32 ± 0.08 (16)
GIK	0.14 ± 0.038 (24)††	0.34 ± 0.11 (10)††	1.34 ± 0.34 (12)	1.83 ± 0.18 (15)
P	NS	NS	<0.015	<0.015

Values expressed as mean ± standard error of the mean with number of samples in parentheses.

P values indicate differences between dogs without infusion and dogs given glucose-insulin-potassium. $*P < 0.05$; $**P < 0.005$ for comparison between control dogs (no ligation) and dogs without infusion; $\dagger P < 0.05$, $\dagger\dagger P < 0.005$ for comparison between control dogs (no ligation) and dogs given glucose-insulin-potassium infusion.

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; CP = creatine phosphate; NS = not significant; *P* = probability; Pi = inorganic phosphate.

For explanation of biopsy zones, see Figure 1.

TABLE VIII

Effect of Infusions of Glucose-Insulin-Potassium (GIK) of 6 Hours' Duration on Endocardial and Epicardial Metabolic Values in Infarct Zones

	Values (μmole/g wet weight)	
	Endocardial	Epicardial
ATP		
No GIK	0.53 ± 0.19 (16)	1.15 ± 0.35 (16)
GIK	1.46 ± 0.39 (17)	1.71 ± 0.41 (17)
P	<0.04	NS
Pi		
No GIK	10.99 ± 1.00 (15)	10.78 ± 1.27 (15)
GIK	7.91 ± 0.96 (17)	8.95 ± 1.27 (17)
P	<0.03	NS
K^+/Na^+		
No GIK	0.48 ± 0.06 (25)	0.47 ± 0.04 (24)
GIK	0.49 ± 0.07 (34)	0.67 ± 0.07 (34)
P	NS	<0.03
Glycogen*		
No GIK	9.1 ± 1.8 (26)	11.6 ± 1.8 (26)
GIK	15.2 ± 2.5 (35)	22.1 ± 2.3 (35)
P	NS	<0.001

*As glucose equivalents.

Values expressed as mean values ± standard error of the mean with number of samples in parentheses.

ATP = adenosine triphosphate; NS = not significant; *P* = probability; Pi = inorganic phosphate.

moglobin concentration. The cause of the latter is not clear, but hemodilution must be considered. Plasma proteins and plasma albumin both decreased after coronary artery ligation, but results were not different in the dogs with and without infusion. However, blood urea decreased more in the dogs treated with glucose-insulin-potassium than in untreated dogs. Hemodilution may be associated with decreased S-T elevation in experimental ischemia,[32] but the degree of hemodilution used was profound. Whatever the mechanisms involved, it appears that decreased free fatty acid extraction might not be the only cause of decreased O_2 extraction after glucose-insulin-potassium infusion.

Glucose-insulin-potassium and anaerobic glycolysis: One postulated mode of action of glucose-insulin-potassium may be increased anaerobic glycolysis.[1,11] As judged by multiple biopsy samples, glucose-insulin-potassium caused relatively small changes in high energy phosphate compounds and lactate, with more definite increases in glycogen in the infarct zone. A simultaneous increase in tissue contents of high energy phosphate compounds, lactate and glycogen in ischemic tissue could suggest that increased glucose uptake had been accompanied by increased net conversion to glycogen and lactate and increased adenosine triphosphate production. These changes are compatible with but do not prove increased anaerobic glycolysis during glucose-insulin-potassium infusion. When compared with the estimated glucose uptake, rates of anaerobic glycolysis (with lactate production) would be low and unlikely to contribute significantly to the energy deficit developing in the infarcting myocardium.[26] However, increased *aerobic* glycolysis could act in two ways. First, some evidence suggests that glycolytically produced ATP may have a special role in the maintenance of membrane integrity.[33] Second, increased oxidative metabolism of glucose may be associated with decreased ischemic damage.[45]

An increased content of tissue glycogen could occur either by decreased breakdown or increased synthesis of glycogen. Activation of phosphorylase required for breakdown of glycogen occurs in response to increased intracellular contents of inorganic phosphate and of adenosine monophosphate or by a cyclic-AMP mediated interconversion of phosphorylase *b* to *a*, or both.[34] In our experiments, inorganic phosphate decreased as a result of glucose-insulin-potassium infusion, raising the possibility of decreased breakdown of glycogen. On the other hand, increased synthesis of glycogen could readily be explained as the combined effect of increased glucose uptake and the action of insulin.[34] Increased glycogen stores are known to protect against subsequent anoxia[5,35] although there is no firm evidence that increased glycogen protects against myocardial ischemic damage.

The amount of increase in the glucose uptake required to cause the glycogen increases found would be about 2 μmole/g wet weight per hour. At an assumed coronary flow rate of 1 ml/g per min,[36] the glucose uptake of the dog heart before ligation can be estimated at about 20 μmole/g wet weight per hour from our arteriovenous difference data. With a mean coronary blood flow of about 20 percent of normal to the peripheral infarct zone[26] the mean glucose uptake of that zone would be at least 4 μmole/g wet weight per hour in hearts without infusion and about 12 μmole in hearts with glucose-insulin-potassium infusion. Larger values for glucose uptake would be obtained if the arteriovenous differences across the infarcting tissue were greater than the arterial coronary sinus differences.[15] Lactate formation was not the major fate of the glucose uptake according to oxygen extraction ratio data (Table I), even in the infarcting tissue as shown by studies with carbon-14–labeled glucose.[15] Hence the major part of the glucose taken up during glucose-insulin-potassium infusion is probably metabolized oxidatively, a conclusion that also argues against an important role for anaerobic glycolysis in the action of glucose-insulin-potassium infusion.

Effects of glucose-insulin-potassium and free fatty acid metabolism: Uptake and metabolism of free fatty acids by the infarcting tissue may lead to less efficient utilization of oxygen than with glucose as substrate. First, free fatty acids have a lower phosphorylation/oxidative ratio than glucose when normally oxidized, but the magnitude of this effect is only about 10 percent if the phosphorylation/oxidative ratio falls from 3.15 (glucose) to about 2.85 (free fatty acid) on changing from oxidation of only glucose to only free fatty acid. But in the present experiments, free fatty acids accounted for only about 20 percent of the oxygen extraction ratio in hearts without infusion; hence, such phosphorylation/oxidative changes could not be important. However, Bremer[37] has postulated a theoretical back-reaction that could occur during the oxidation of fatty acids so that the effective phosphorylation/oxidative ratio could be as low as 1. Second, it has frequently been suggested that intracellular free fatty acids

could accumulate in ischemic tissue[38] with uncoupling of oxidative phosphorylation, but firm evidence to back this hypothesis is lacking. Third, there is in ischemic tissue an accumulation of acyl CoA, which is an intermediate of fatty acid oxidation; acyl CoA inhibits transfer of energy as adenosine triphosphate from within to without the mitochondria[39] and therefore impairs the effective production of energy from oxygen. These effects would explain why decreased circulating free fatty acid and decreased free fatty acid extraction could be an important effect of glucose-insulin-potassium infusion.

Effects of glucose or insulin, or both, at a relatively constant circulating free fatty acid concentration[23] have been found in an isolated rat heart system where enzyme release is decreased, thus suggesting that glucose-insulin-potassium infusion could also have a "membrane-stabilizing" effect. We have no evidence for or against the possibility that glucose-insulin-potassium acted as a "polarizing" agent, as originally suggested by Sodi-Pallares et al.[40]; although S-T elevation decreased in the infarct zone, the degree of K^+ depletion was not altered by glucose-insulin-potassium although K^+ increased in the periinfarct border zone. However, the techniques used did not allow precise separation of intra- and extracellular K^+ values.

Comparison with baboon model: The similarities between the effects of glucose-insulin-potassium infusion in dogs and baboons[8] were an increased tissue K^+/Na^+ ratio in periinfarct zones and some infarct zones, an increased glycogen in most zones, and some improvement in high energy phosphate or inorganic phosphate values in the infarct zone. A difference was a small increase in the lactate content in the central infarct zone in the dog. In both dog and baboon models major changes in the K^+/Na^+ ratio and glycogen content could be found in zones where there was no evidence for increased anaerobic glycolysis, but the dog data suggest increased aerobic glycolysis. An unexplained discrepancy was an increase of inorganic phosphate in the nonischemic zone in the baboon but a decrease in the dog. In our dog model, in contrast to the baboon, the nonischemic zone underwent only minor changes after coronary arterial ligation. In both models, glucose-insulin-potassium was more effective in the peripheral and periinfarct zones than in the central infarct zone, suggesting that it affects zones of milder rather than of more severe ischemia. However, the infarction process after occlusion of the left anterior descending artery in the dog is heterogeneous (Fig. 4); in spite of multiple biopsies, the methods used in our study do not allow quantification of the effects of glucose-insulin-potassium on infarct size.

Electrocardiographic effects of glucose-insulin-potassium: In the dog, glucose-insulin-potassium hastened the rate of decrease of epicardial S-T elevation found in infarct zones; this is believed to be the first evidence suggesting that observation of epicardial S-T changes over a long period (6 hours in this case) could be a useful index of increased tissue metabolic improvement. By extrapolation, precordial changes similar in direction could be expected.[12] However, the S-T segment changes over the infarct zone were relatively large, whereas tissue metabolic effects were less marked. In addition, major metabolic changes were found in the periinfarct zone in contrast to the absence of electrocardiographic changes. Our data on dogs suggest that glucose-insulin-potassium improves both electrocardiographic and tissue metabolic features of infarction, but there is no exact correspondence between these changes. Smith et al.[36] have noted that the degree of S-T elevation and the severity of reduction in flow do not always correlate well. In the baboon, glucose-insulin-potassium caused tissue metabolic improvement without decreasing epicardial S-T elevation.[8] Spontaneous fluctuations in the evolution of epicardial S-T changes could contribute to the differences at 6 hours between the groups with and without infusion; hence, for firm interpretation, intermediate S-T values between 30 minutes and 6 hours are required. It is not possible to say whether the dog or baboon model corresponds more closely to the situation in patients with acute myocardial infarction, and further exploration of the possible use of electrocardiographic changes to monitor the effects of glucose-insulin-potassium both in man and in experimental animals is required. In particular, the epicardial electrocardiogram could be used to test whether glucose-insulin-potassium might differentially affect zones of moderate rather than of severe electrocardiographic damage.

Application to assessment of effects of glucose-insulin-potassium in patients: There are many outstanding questions to be answered before glucose-insulin-potassium can be recommended for general use in patients with acute myocardial infarction.[41] Our studies cannot be applied directly to patients, especially because there were basal lactate, free fatty acid and albumin values that would be unusual in patients with acute myocardial infarction.[29,42] Nevertheless, the effects reported here constitute further evidence for a beneficial effect of glucose-insulin-potassium on tissue metabolic, histologic and electrocardiographic criteria of ischemic damage. The association between increased glucose and decreased free fatty acid arteriovenous differences across the whole heart with simultaneous tissue metabolic improvement after glucose-insulin-potassium suggest that monitoring of arterial and arteriovenous substrate differences in patients with acute myocardial infarction given glucose-insulin-potassium might be a useful procedure, as already reported in patients with stable coronary artery disease or unstable angina by others.[9,43] It is also of interest that other agents that reduce myocardial extraction of free fatty acid and increase that of glucose, such as propranolol[18,44] and dichloroacetate,[45] decrease myocardial ischemic damage as evidenced pathologically or by decreased epicardial S-T elevation. There is thus increasing evidence to support the view that provision of glucose is beneficial[1,2,7,9] and provision of free fatty acids harmful[38,46] to infarcting myocardium.

However, these hypotheses need vigorous evaluation in man. The effects of glucose-insulin-potassium given 30 minutes after acute coronary occlusion and studied 6 hours later might differ from results with treatment

later in evolving human myocardial infarction. Rackley et al.[47,48] found a beneficial effect of glucose-insulin-potassium in patients with acute myocardial infarction, judged both by mortality and by enzyme release. However, Reduto et al.,[49] found no effect of glucose-insulin-potassium on infarct size measured by the creatine phosphokinase curve technique. Heng et al.[50] gave glucose-insulin-potassium infusions to patients in the acute stage of myocardial infarction and failed to find any statistically beneficial effect; they discontinued their trial. The blood sugar levels reached in their study (over 30 millimolar) apparently caused a positive inotropic effect, which is known to increase infarct size. It follows that future trials of glucose-insulin-potassium in man should avoid such high blood sugar levels or increase the dose of insulin relative to that of glucose; in our study the mean blood sugar was just over 10 millimolar.

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Analysis of Wall Dynamics and Directional Components of Left Ventricular Contraction in Man

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The extent and rate of left ventricular wall thickening during systole has previously been shown to be a useful measure of regional ventricular function and to play an important role in the ejection of blood from the left ventricle. The relation among systolic wall thickening, the directional components of contraction, ejection fraction and force velocity measurements is therefore of interest in understanding the dynamics of contraction of the intact ventricle. This report describes a theoretical basis and method for using ventricular angiograms to quantify the separate contributions of longitudinal shortening, circumferential shortening and systolic wall thickening to overall ventricular performance in man. One hundred twenty-two patients with valvular, coronary or myocardial heart disease were studied with biplane angiocardiography during diagnostic cardiac catheterizations. The percent contribution of directional components to total work or power developed by a mid-wall equatorial element of myocardium was shown to be: longitudinal, 14 percent in normal and diseased ventricles; circumferential, 45 percent in normal, increasing to 55 percent in dilated ventricles ($P < 0.005$); wall thickening, 40 percent in normal, decreasing to 31 percent in dilated ventricles ($P < 0.001$). Thus, left ventricular contraction, which is expressed as systolic wall thickening, quantified separately from inward wall displacement due to mid-wall circumferential shortening, accounts for nearly half of segmental left ventricular work and power. The rate and extent of ventricular wall thickening correlated closely with ejection fraction ($r = 0.92$ and 0.95, respectively) and with velocity of circumferential shortening ($r = 0.90$ and 0.80, respectively). Previous models of ventricular and myocardial mechanics that include computations of mid-wall longitudinal and circumferential stress and strain do not appear to account for the large contribution of systolic wall thickening to the performance of the intact heart. Force-velocity relations as heretofore described may therefore be partial descriptors of myocardial function in the intact ventricle.

Myocardial performance in the intact left ventricle has been evaluated in terms of extent and velocity of shortening with respect to wall forces or stresses in equatorial and meridional directions. More recently, the extent and velocity of wall thickening during ventricular systole have been shown to be reduced in myocardial disease. In this study left ventricular wall performance in man is examined with a consideration of each of these components, namely, the amount and rate of wall thickening as well as circumferential and meridional extent and velocity of shortening in relation to their respective wall forces.

In experimental animals the extent and rate of left ventricular wall thickening during systole have been measured during hemodynamic manipulations including regional myocardial ischemia, pharmacologically altered contractility and changes in preload or afterload. Hawthorne[1] and Cothran et al.[2] found that thickening of the ventricular wall contributed significantly to the decrease in intraventricular volume

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during ejection; with isoproterenol there was a disproportionately larger increase in left ventricular wall thickness compared with changes in circumference during ejection. Mitchell et al.[3] showed that the amount of systolic wall thickening was greatly influenced by the Frank-Starling mechanism and by norepinephrine infusion. Using metallic markers on the ventricular endocardium, these investigators also demonstrated trabecular infolding of the endocardium into the ventricular cavity. This finding explains why apparent wall thickening measured directly on angiographic films may overestimate anatomic wall thickening. In addition, their data indicate that wall thickening and trabecular infolding play an important role in the dynamic geometry of ventricular ejection. Hugenholtz et al.[4] and Rackley et al.[5] have developed a technique for accurately calculating wall thickness throughout systole based on end-diastolic wall thickness and assuming constant myocardial mass. Liedtke et al.[6] reported that the extent of left ventricular wall thickening in experimental animals increased with a fall in aortic pressure and decreased with a rise in aortic pressure, but was little affected by preload. Nitroglycerin markedly increased wall thickening, probably by reducing afterload. Leshin et al.[7] found a linear, direct correlation between extent of wall thickening and ejection fraction during various types of anesthesia that depressed myocardial function. Heikkila et al.[8] reported that the extent and rate of wall thickening sharply separated areas of regional myocardial dysfunction from normal areas and were more sensitive than changes in epicardial segment shortening regardless of whether cardiac function was depressed by ischemia or enchanced by isoproterenol. Goldstein and deJong[9] concluded that myocardial wall thickening was more sensitive than the first derivative of left ventricular pressure (dP/dt) or pressure-derived Vce (peak velocity of the contractile element) as a measure of local changes in myocardial function during regional ischemia. deJong and Goldstein[10] found a direct quantitative correlation between localized changes in wall thickening and the severity of regional ischemia assessed by lactate production and inosine concentration in the regional venous drainage of the myocardium affected.

In man, left ventricular wall thickening has also been examined as a measure of myocardial dysfunction. Gault et al.[11] reported that left ventricular wall thickness during systole increased by an average of 32 percent in six patients without and 23 percent in nine patients with left ventricular disease. Bunnell et al.[12] found that three patients with reduced ejection fraction also had reduced wall thickening compared with findings in five normal subjects. Wall thickening was increased in four patients with outflow obstruction whose ejection fraction was greater than that of the normal group. Eber et al.,[13] in three patients, observed greatly reduced systolic wall thickening in localized areas of paradoxic expansion in the diseased left ventricle. Dumesnil et al.[14] correlated the regional rate of wall thickening with localized areas of left ventricular hypokinesia, akinesia or dyskinesia. The severity of abnormal wall dynamics correlated closely with evidence of myocardial infarction in the electrocardiogram and with the anatomic severity and distribution of coronary artery disease observed in coronary arteriograms. Dodge et al.[15] calculated that the displacement of intraventricular blood due to wall thickening during systole represented nearly 50 percent of ventricular stroke volume in normal man. This percent was higher in patients with aortic stenosis because of increased systolic wall thickening and was lower in patients with impaired dilated ventricles due to reduced wall thickening during systole.

These previous studies suggest that ventricular contraction that appears as systolic wall thickening plays an important but largely undefined role in the mechanical function of the intact ventricle. In particular, the relations between systolic wall thickening, the directional components of contraction, the ejection fraction and force-velocity measurements are of interest in understanding ventricular dynamics during systole. This report describes a theoretical basis and approach for assessing the separate contributions of longitudinal shortening, circumferential shortening and wall thickening to the work and power of a midwall segment of the left ventricle. The results from 122 patients with valvular, coronary or primary myocardial disease are presented and show the importance of wall thickening in relation to circumferential and longitudinal components of contraction.

Methods

Data from 122 patients undergoing diagnostic cardiac catheterization for evaluation of cardiovascular disease at the Veterans Administration Hospital in Seattle were analyzed. After informed consent was obtained, patients were studied in the supine position with use of local anesthesia. Left ventricular pressure recordings were obtained using carefully flushed no. 8F Gensini or 8.5F transseptal catheters. Three types of solid state microdisplacement external pressure transducers were utilized: the Kulite PSL 125-6, the Micron MP-15 and the Microdot MS-5-S pressure transducers. On occasion a Statham P23Gb strain gauge was employed. These catheter manometer systems tested in vitro on a sine wave pressure generator had uniform amplitude responses to 20 hertz with resonant frequencies over 100 hertz.[16]

Left ventricular dimensions and volumes were determined by the length-area method[17] from biplane angiocardiographic films using an Elema-Schonander film changer at a filming rate of 12/sec. Left ventricular mass was determined from end-diastolic biplane films as previously described.[5] The method has been validated in this laboratory by comparison with postmortem left ventricular weights.[18] Left ventricular wall thickness throughout systole was calculated from instantaneous anteroposterior and lateral internal radii and end-diastolic ventricular mass assuming an ellipsoid model and constant ventricular mass during the heart cycle as previously described.[4,5] This procedure has been experimentally validated by Sanmarco and Davila.[19] All dimensional data were obtained from the first two or three cycles after injection of contrast medium so that the measurement of ventricular size or function would not be affected by the medium.[20]

Left ventricular dimensions (length, radii in anteroposterior and lateral views, wall thickness) and pressures were digitized for computer processing on a Control Data Corporation computer, model 6400. Digitized pressures were high fre-

quency-limited by a digital low pass filter with a cutoff frequency of 30 hertz. Digitized volume data were filtered by a low pass digital filter that had linear attenuation from 3 hertz to a cutoff point of 6 hertz. These frequency limits for filtering dimension data were chosen to reduce methodologic random variations or "static" yet retain faithful wave forms of ventricular dimensions throughout the heart cycle. Fourier analysis of ventricular volume curves in this laboratory indicated that these frequency limits were optimal for obtaining accurate mathematically smooth volume and dimension curves for purposes of differentiation. Our results agree with those of Vayo,[21] who also studied ventricular volume curves using Fourier analysis. All curves of pressure, ventricular dimensions and volume during a heart cycle were filtered, regenerated by computer and derived variables calculated every 0.01 second. Brooks et al.[22] described digital filtering of ventricular volume curves obtained from angiograms; their detailed analysis and comparison with simultaneous velocity measurements with cathether instruments have documented the accuracy of computer-processed angiographic data.

The pump power developed by the left ventricle has been used to describe the overall pump function of the ventricle in man[23] but has not permitted assessment of the separate directional components contributing to ventricular pump power. In this study equations for the power developed by a sample element of left ventricular wall were derived based on wall stresses and rate of change in ventricular dimensions determined from left ventricular pressures and angiograms. These equations permitted calculations of the work and power generated by the sample element in longitudinal, circumferential and radial (due to wall thickening) directions.

Calculations of ventricular wall element power: The theory for calculating left ventricular wall element power requires setting up reference coordinates with an origin at the center of a 1 cm^3 element of myocardium located at the midwall of the ventricle (Fig. 1). The contractile behavior of the element is described in each direction by the velocity of contraction along the reference coordinates and by the wall stress developed on each face of the cube perpendicular to each coordinate. The work and power generated by the element of ventricular wall can therefore be analyzed in terms of meridional (longitudinal), equatorial (circumferential) and radial (wall thickening) components. Total elemental power is calculated as the sum of components generated at the faces of the cube where each component is the instantaneous product of stress and velocity normal to each face of the cube.

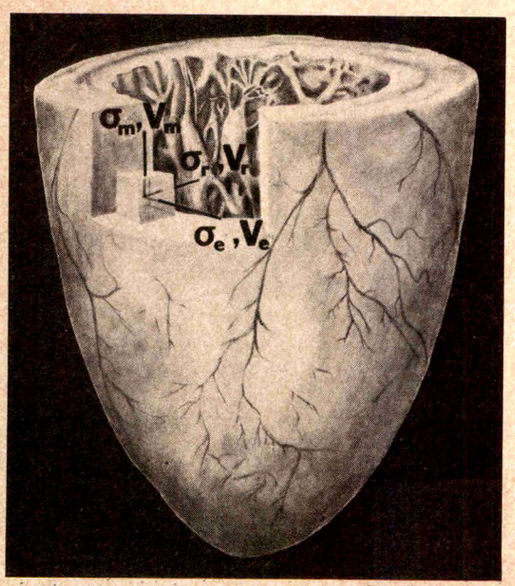

FIGURE 1. Schema of the sample element and reference coordinates of the left ventricular wall. Wall stresses in meridional (σ_m), equatorial (σ_e) and radial (σ_r) directions and velocities in meridional (V_m), equatorial (V_e) and radial (V_r) directions are indicated.

The radial component in particular requires further consideration before proceeding. This component of element power arises because the wall thickens as circumferential shortening occurs. Because the wall thickens against left ventricular pressure, it generates power and work in the process of displacing ventricular contents.

As an initial illustration of the significance of the radial component, consider the following hypothetical papillary muscle strip. With contraction it shortens a distance, Δl, against a load, F, and does work of $\Delta l \times F$. In the process of shortening, the muscle thickens since total volume of the muscle strip remains constant. However, because this thickening is done freely without opposing side pressure, no energy is expended in thickening and no component of work is developed in thickening as such. Now consider the muscle contracting the same distance against the same force in the presence of a side pressure or restriction applied to the papillary muscle strip (imagine a segment of rubber tubing fitting snugly around the muscle). Thickening then requires energy, and the total work done by the muscle has two components: $\Delta l \times F$ plus a component related to the product of pressure and thickening. In the intact ventricle each fiber faces an analogous situation. In addition to the tension exerted at the ends of the contracting fiber, the side pressure or intramyocardial tissue pressure requires that energy be expended in order for the fiber, and hence the ventricular wall, to thicken. Thus, there is a component of work due to wall thickening that is not measured and accounted for by the longitudinal shortening and force. There is also a component of power, or rate of doing work, associated with this thickening.

Component of ventricular work due to wall thickening: Proof of this concept in the intact heart would require determination of pump power of the ventricle and independent determination of each of the three directional components of element power, or rate of doing work. Pump power must then equal the sum of the three elemental components integrated throughout the wall volume of the ventricle. At present there are no reasonably simple technical methods or mathematical equations for accomplishing this task in a thick-walled ellipsoid model of the ventricle. However, mathematical proof may be demonstrated for a thick-walled cylinder as an illustration of the validity of the concept. The detailed equations presented in the Appendix* show that the external pump power delivered to blood contained within the cylinder is exactly equal to the sum of the circumferential component (due to circumferential shortening) plus the radial component (due to wall thickening). Consideration of the circumferential component alone fails to account for all of the work and power developed on the contents of the cylinder. Thus, to obtain a complete description of performance of the wall element, it is necessary to consider the radial component separately and in addition to the circumferential component. It should be reiterated that the power of the sample element can easily be calculated for an ellipsoid of revolution; it is the proof of the separateness of the radial component that is difficult in an

* Published with the reprints of this article and available from the author on request.

ellipsoid and this proof has therefore been demonstrated for a thick-walled cylinder.

Meridional, equatorial and radial components of work or power: For the cubic element at the mid-wall of the left ventricle, it was necessary to calculate three components of work or power: meridional (longitudinal), equatorial (circumferential) and radial (wall thickening). To compute these components, stresses and velocities in each of the three directions were determined as follows.

Meridional stress (σ_m) and equatorial stress (σ_e) were computed as previously derived by Sandler and Dodge.[24] Stress in the radial direction (σ_r) is directly related to the pressure within the wall against which myocardial fibers thicken, namely, intramyocardial tissue pressure. Since the cubic element is at the mid-wall between epicardium and endocardium, the radial stress is equal to mid-wall myocardial tissue pressure, previously shown to be approximately equal to intraventricular pressure.[25–27] Radial stress therefore equals left ventricular pressure.

The three components of velocity were also derived in order to compute elemental power. In meridional and equatorial planes the velocities are computed from the respective mid-wall circumferential shortening velocities. The normalized meridional (v_m) and equatorial (v_e) velocities are given by the equations:

$$v_m = \frac{1}{C_m}\frac{dC_m}{dt}$$

$$v_e = \frac{1}{C_e}\frac{dC_e}{dt}$$

where C_m and C_e are elliptical circumferences in meridional and equatorial planes, respectively. These circumferences were calculated by the equation:

$$C = 2\pi\sqrt{\frac{\left(A+\frac{h}{2}\right)^2+\left(B+\frac{h}{2}\right)^2}{2}}$$

where A and B are, respectively, the major and minor axes of each ellipse and h is the wall thickness. In the equatorial plane, A and B are the shortest and longest internal ventricular radii, determined from anteroposterior and lateral films by the length-area method. In the meridional plane, A is one half of the longest internal ventricular length from anteroposterior and lateral films; B is the root mean square of the internal minor radii according to the following equation:

$$B_{meridional} = \sqrt{\frac{R_{ap}^2 + R_{lat}^2}{2}}$$

The derivatives of C with respect to time were determined by computer by the method of central differences. In an analogous manner, normalized velocity in the radial direction is given by the equation:

$$v_r = \frac{1}{h}\frac{dh}{dt}$$

where h is left ventricular wall thickness.

From the values of stress and shortening velocity in each of the three directions, instantaneous total elemental power (or per unit volume of element since the element was defined as 1 cm^3) is given by the equation:

$$Pwr = \sigma_m v_m + \sigma_e v_e + \sigma_r v_r$$

where each of the terms is described above. Values of average element power were determined by averaging instantaneous element power through systole and are presented in this report. Stroke work of each element was determined by integrating instantaneous power over systole.

Elemental power and work, wall stresses and shortening velocities were calculated from computer-smoothed, regenerated pressure and dimension data obtained at every 10 msec interval throughout the heart cycle for each of 122 patients studied.

Case Material

The 122 patients in this study were grouped as follows:

Group A: Twelve patients without heart disease. These patients had normal coronary arteriograms and left ventricular hemodynamics.

Group B: Nineteen patients with coronary artery disease by arteriography whose biplane ventricular angiograms revealed no localized or segmental dysfunction.

Group C: Twenty patients with coronary artery disease by arteriography whose biplane ventricular angiograms revealed localized areas of akinesia or dyskinesia.

Group D: Fifteen patients with severe, usually three vessel, coronary artery disease and generalized hypokinesia of the left ventricle. Since it was difficult to distinguish between a diffusely hypokinetic ventricle and one with multiple dyskinetic areas, patients with an ejection fraction of 26 percent or less were classified as having diffuse hypokinesia.

Group E: Nineteen patients with primary nonobstructive myocardial disease. These patients had normal coronary arteries, increased ventricular mass and grossly abnormal left ventricular hemodynamics.

Groups F to I: Thirty-seven patients with cardiac valve disease and various degrees of ventricular dysfunction. They were classified by type of lesion regardless of status of myocardial function as follows: F, aortic stenosis; G, aortic insufficiency; H, mitral stenosis; I, mitral regurgitation. There were small numbers of patients in the groups with mitral valve disease because patients in atrial fibrillation were excluded from the analysis.

Groups A, B, C, D and E, in that order, represent patients with progressively severe, purely myocardial dysfunction and were separable on the basis of coronary arteriographic findings

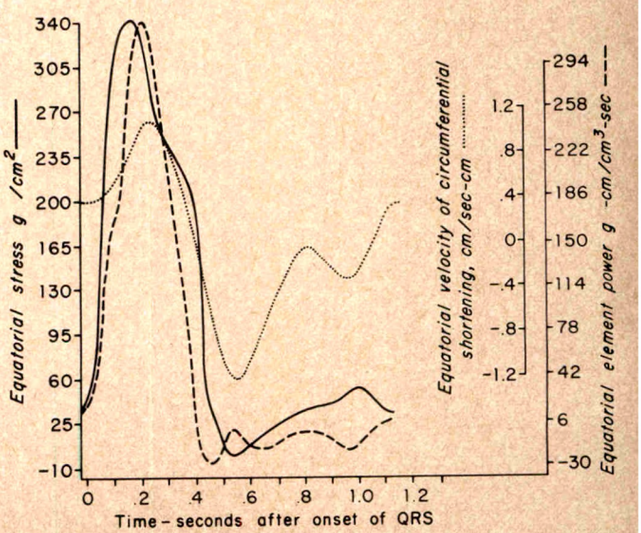

FIGURE 2. Normal patient. Time course during the cardiac cycle of circumferential wall shortening and circumferential stress and their instantaneous product, equatorial element power.

and the presence of localized dyskinetic areas or diffuse hypokinesia of the left ventricle. These patients were grouped together to avoid the problem of assessing ventricular performance in the presence of cardiac valve malfunction. Groups F to I represent patients with chronic volume or pressure overload, or both, due to valve dysfunction and were classified by type of lesion regardless of ventricular function to demonstrate the value of wall element analysis in the presence of valve disease. Patients were placed in these groups without knowledge of the values of stress, contraction velocities, element power or other measures of myocardial "contractility."

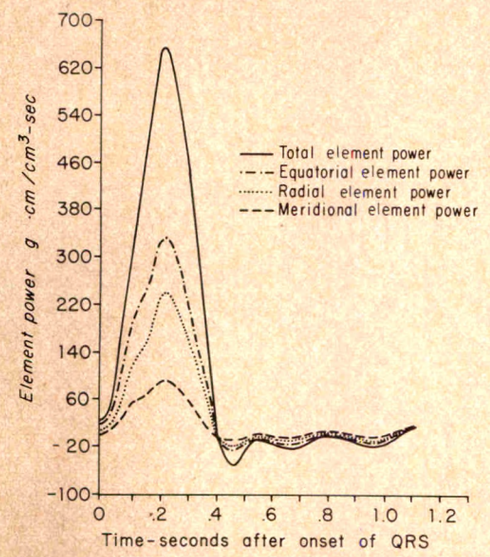

FIGURE 3. Same patient as in Figure 2. Time course during the cardiac cycle of equatorial, meridional and radial element power with their instantaneous sum, total element power.

Results

Equatorial wall stress and normalized velocity of equatorial shortening for a patient with normal coronary arteriograms and ventricular function are shown in Figure 2. The instantaneous product of the stress and velocity is equatorial wall element power; it peaks early in systole. Similar curves for meridional and radial element power were added to the equatorial component to obtain total instantaneous wall element power throughout the heart cycle for the same patient (Fig. 3).

The mean values and standard deviations of selected quantitative angiographic data are given in Table I. End-diastolic volume and mass were increased in every group with heart disease. Stroke volume and work changed appropriately for myocardial or valve dysfunction. The ratio of stroke work to left ventricular mass was a measure of work performed per gram of left ventricle. It deteriorated with diminished myocardial function and was normal in valve dysfunction with hypertrophy despite greatly elevated values for total stroke work.

Table II shows the mean values of various measurements of ventricular function in each group of patients.

TABLE I

Hemodynamic and Angiographic Data

	Group A Normal (no. = 12)	Group B CAD: Abnormal Coronary Arteries Only (no. = 19)	Group C CAD: Local Dyskinesia (no. = 20)	Group D CAD: General Hypokinesia (no. = 15)	Group E Severe PMD (no. = 19)	Group F Aortic Stenosis (no. = 12)	Group G Aortic Regurgitation (no. = 16)	Group H Mitral Stenosis (no. = 6)	Group I Mitral Regurgitation (no. = 3)
ED volume index (cc/m^2)	72 ± 16	78 ± 16 NS	98 ± 33 $t = 2.5$ $P < 0.02$	150 ± 31 $t = 7.8$ $P < 0.001$	163 ± 28 $t = 10.2$ $P < 0.001$	97 ± 19 $t = 3.5$ $P < 0.005$	189 ± 46 $t = 8.3$ $P < 0.001$	105 ± 21 $t = 3.7$ $P < 0.005$	158 ± 38 $t = 6.4$ $P < 0.001$
Stroke volume index (cc/m^2)	42 ± 11	40 ± 8 NS	37 ± 10 NS	29 ± 7 $t = -3.6$ $P < 0.005$	31 ± 9 $t = -3.0$ $P < 0.01$	50 ± 13 NS	77 ± 25 $t = 4.5$ $P < 0.001$	48 ± 22 NS	50 ± 15 NS
Stroke work index (g-m/m^2)	56 ± 13	59 ± 16 NS	52 ± 13 NS	32 ± 11 $t = -5.3$ $P < 0.001$	35 ± 11 $t = -4.8$ $P < 0.001$	97 ± 39 $t = 3.4$ $P < 0.005$	110 ± 31 $t = 5.6$ $P < 0.001$	64 ± 37 NS	61 ± 16 NS
LV mass index (g/m^2)	93 ± 19	108 ± 20 $t = 2.1$ $P < 0.05$	117 ± 30 $t = 2.5$ $P < 0.02$	159 ± 49 $t = 4.4$ $P < 0.001$	185 ± 36 $t = 8.1$ $P < 0.001$	186 ± 71 $t = 4.4$ $P < 0.001$	210 ± 58 $t = 6.7$ $P < 0.001$	114 ± 20 $t = 2.1$ $P < 0.05$	240 ± 131 $t = 4.2$ $P < 0.005$
Stroke work/LV mass (g-m/g)	0.62 ± 0.14	0.55 ± 0.17 NS	0.46 ± 0.15 $t = -3.0$ $P < 0.01$	0.20 ± 0.05 $t = -11.1$ $P < 0.001$	0.19 ± 0.05 $t = -12.2$ $P < 0.001$	0.55 ± 0.19 NS	0.56 ± 0.21 NS	0.59 ± 0.38 NS	0.32 ± 0.21 $t = -3.1$ $P < 0.01$
Peak equatorial stress (g/cm^2)	358 ± 74	355 ± 55 NS	382 ± 68 NS	416 ± 100 NS	387 ± 63 NS	384 ± 96 NS	458 ± 113 $t = 2.7$ $P < 0.01$	413 ± 101 NS	324 ± 94 NS
Wall thickness change, (%) ED to ES	45 ± 8	37 ± 9 $t = 2.2$ $P < 0.05$	27 ± 8 $t = 6.2$ $P < 0.001$	12 ± 3 $t = 14.7$ $P < 0.001$	12 ± 4 $t = 14.9$ $P < 0.001$	35 ± 15 NS	30 ± 12 $t = 3.6$ $P < 0.005$	36 ± 21 NS	21 ± 11 $t = 4.1$ $P < 0.005$

Values shown are mean ± 1 standard deviation with the significance or nonsignificance (NS) of each group compared with normal subjects by Student's t test.[28] CAD = coronary artery disease; ED = end-diastolic; ES = end-systolic; index = per square meter body surface area; LV = left ventricular; P = the probability that the observed difference from normal is due to chance alone; PMD = primary myocardial hypertrophic disease; t = the test statistic of Student's t test.

Ejection fraction sensitively discriminated between normal and abnormal subjects, and its use yielded high t values. Table II also shows values for the normalized velocities of mid-wall shortening in equatorial and meridional directions, as well as velocity of wall thickening, here termed the radial velocity. Each of the three velocity components separated the normal from the abnormal groups, but the velocity of wall thickening was the most sensitive of the three variables. Its ability to separate normal patients from those with only abnormal coronary arteries (Group B) ($P < 0.05$) was comparable with that of ejection fraction.

The velocity of wall thickening during systole correlated closely with the ejection fraction ($r = 0.92$) (Fig. 4). It also correlated with the velocity of circumferential shortening ($r = 0.90$) but not with values of equatorial wall stress ($r = -0.09$). Percent wall thickening during systole also correlated closely with ejection fraction ($r = -0.95$) and velocity of circumferential shortening ($r = -0.80$) (not illustrated).

Table III gives the mean values of total average element power and of the components in each direction. The equatorial component was the largest. Values in the radial direction, resulting from wall thickening separate from inward displacement due to circumferential shortening, comprised a major portion of total element power. The meridional component due to longitudinal shortening was the smallest.

The relative contribution of each directional component as percent of total average element power is given in Table IV. Data shown were determined as the mean of the percent values for individual cases. The equatorial component accounted for 45 percent of total element power in normal subjects and increased to 55 percent of the total ($P < 0.005$) in patients with ventricular dilatation due to severe myocardial dysfunction. The radial component, due to wall thickening, accounted for 40 percent of the total in normal subjects and decreased to 31 percent ($P < 0.001$) in patients with dilated ventricles. The meridional component accounted for 14 percent of the total in normal and dilated ventricles. Thus, in normal subjects the radial component was almost as large as the equatorial component

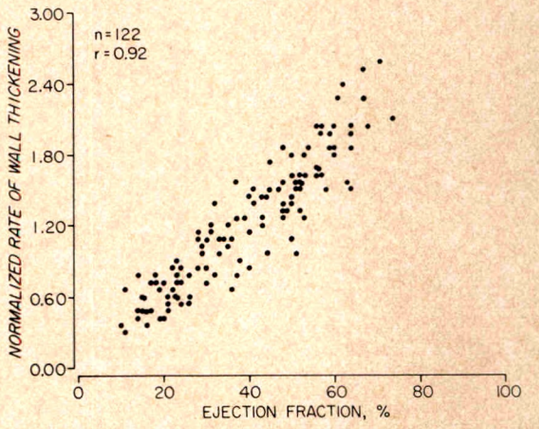

FIGURE 4. Correlation of ejection fraction with rate of wall thickening during left ventricular contraction.

TABLE II

Left Ventricular Function

	Group A	Group B	Group C	Group D	Group E	Group F	Group G	Group H	Group I
Ejection fraction (%)	58 ± 6	52 ± 8 $t = -2.2$ $P < 0.05$	40 ± 8 $t = -6.9$ $P < 0.001$	19 ± 4 $t = -19.3$ $P < 0.001$	20 ± 6 $t = -17.2$ $P < 0.001$	53 ± 15 NS	41 ± 11 $t = -4.7$ $P < 0.001$	45 ± 16 $t = -2.4$ $P < 0.05$	33 ± 13 $t = -4.9$ $P < 0.001$
Peak shortening velocity (cm/sec-cm)									
Equatorial	0.98 ± 0.16	0.87 ± 0.24 NS	0.74 ± 0.18 $t = -3.7$ $P < 0.001$	0.38 ± 0.10 $t = 11.8$ $P < 0.001$	0.37 ± 0.13 $t = -11.5$ $P < 0.001$	0.95 ± 0.45 NS	0.78 ± 0.25 $P < 0.05$	0.81 ± 0.29 NS	0.55 ± 0.14 $t = -4.1$ $P < 0.005$
Meridional	0.73 ± 0.19	0.64 ± 0.17 NS	0.46 ± 0.17 $t = -4.0$ $P < 0.001$	0.22 ± 0.10 $t = -9.0$ $P < 0.001$	0.20 ± 0.10 $t = -10.0$ $P < 0.001$	0.65 ± 0.31 NS	0.43 ± 0.13 $t = -4.9$ $P < 0.001$	0.56 ± 0.29 NS	0.45 ± 0.19 $t = -2.2$ $P < 0.05$
Peak thickening velocity (radial, LV wall) (cm/sec-cm)	1.81 ± 0.29	1.55 ± 0.36 $t = -2.1$ $P < 0.05$	1.28 ± 0.28 $t = -5.1$ $P < 0.001$	0.63 ± 0.16 $t = -13.5$ $P < 0.001$	0.60 ± 0.17 $t = -14.6$ $P < 0.001$	1.54 ± 0.67 NS	1.29 ± 0.35 $t = -4.2$ $P < 0.001$	1.48 ± 0.54 NS	0.99 ± 0.41 $t = -4.1$ $P < 0.005$
Maximal ejection rate /EDV (cc/sec-cc)	2.8 ± 0.4	2.6 ± 0.6 NS	2.2 ± 0.4 $t = -3.7$ $P < 0.001$	1.1 ± 0.2 $t = -13.2$ $P < 0.001$	1.1 ± 0.3 $t = -13.4$ $P < 0.001$	2.8 ± 1.1 NS	2.1 ± 0.4 $t = -4.4$ $P < 0.001$	2.2 ± 0.6 $t = -2.2$ $P < 0.05$	1.8 ± 0.4 $t = -3.8$ $P < 0.005$
Maximal external pump power/EDV (g-cm/cm^3-sec)	4.1 ± 0.8	4.2 ± 1.1 NS	3.3 ± 0.8 $t = -2.9$ $P < 0.01$	1.4 ± 0.4 $t = -12.0$ $P < 0.001$	1.4 ± 0.5 $t = -11.9$ $P < 0.001$	5.9 ± 2.6 $t = 2.3$ $P < 0.05$	3.4 ± 1.1 NS	3.2 ± 0.9 NS	2.4 ± 0.6 $t = -3.4$ $P < 0.005$
Maximal dp/dt/P (mm Hg/sec-mmHg)	63 ± 24	56 ± 34 NS	53 ± 33 NS	29 ± 14 $t = -4.6$ $P < 0.001$	26 ± 10 $t = -6.0$ $P < 0.001$	38 ± 12 $t = -3.2$ $P < 0.005$	40 ± 27 $t = -2.4$ $P < 0.05$	44 ± 16 NS	42 ± 12 NS

See footnote to Table I for clinical diagnosis and number of patients in each group.
EDV = end-diastolic volume; other abbreviations as in Table I.

TABLE III

Directional Components of Average Element Power (g-cm/cm³-sec)

	Meridional	Equatorial	Radial	Total
Group A	49 ± 17	155 ± 37	137 ± 26	342 ±72
Group B	41 ± 21	126 ± 59	114 ± 54	281 ± 128
	NS	NS	NS	NS
Group C	38 ± 16	120 ± 40	90 ± 25	249 ± 70
	NS	P <0.02	t = −5.2	t = −3.6
			P <0.001	P <0.005
Group D	18 ± 11	72 ± 22	41 ± 8	131 ± 27
	t = −5.7	t = −7.2	t = −13.9	t = −10.5
	P <0.001	P <0.001	P <0.001	P <0.001
Group E	16 ± 8	59 ± 20	36 ± 12	111 ± 33
	t = −7.3	t = −9.4	t = −15.0	t = −12.2
	P <0.001	P <0.001	P <0.001	P <0.001
Group F	35 ± 22	130 ± 65	145 ± 77	310 ± 152
	NS	NS	NS	NS
Group G	48 ± 23	176 ± 60	120 ± 41	344 ± 114
	NS	NS	NS	NS
Group H	50 ± 31	174 ± 89	119 ± 51	342 ± 164
	NS	NS	NS	NS
Group I	33 ± 25	98 ± 55	77 ± 35	207 ± 113
	NS	t = −2.2	t = −3.4	t = −2.6
		P <0.025	P <0.005	P <0.025

See footnote to Table I for clinical diagnosis and number of patients in each group.

TABLE IV

Relative Contribution of Each Directional Component to Average Element Power

	Percent of Total Average Element Power			
	Meridional	Equatorial	Radial	Total
Group A	14 ± 2	45 ± 5	40 ± 5	100
Group B	15 ± 6	45 ± 4	40 ± 5	100
	NS	NS	NS	
Group C	15 ± 5	48 ± 6	37 ± 4	100
	NS	NS	t = −2.7	
			P <0.02	
Group D	14 ± 8	55 ± 10	31 ± 4	100
	NS	t = 3.0	t = −5.7	
		P <0.005	P <0.001	
Group E	14 ± 7	53 ± 7	33 ± 3	100
	NS	t = 3.3	t = −5.7	
		P <0.005	P <0.001	
Group F	12 ± 4	42 ± 6	46 ± 5	100
	NS	NS	t = 2.9	
			P <0.01	
Group G	14 ± 3	51 ± 6	35 ± 5	100
	NS	NS	NS	
Group H	14 ± 5	51 ± 8	35 ± 4	100
	NS	NS	NS	
Group I	15 ± 3	47 ± 7	39 ± 8	100
	NS	NS	NS	

See footnote to Table I for clinical diagnosis and number of patients in each group.

and accounted for large part of total average element power.

In dilated, diseased ventricles the contribution of wall thickening to total element power became less whereas the contribution due to circumferential shortening became greater. As indicated by the equations in the Appendix, a relatively thick-walled small ventricle should theoretically have a larger radial component than a thin-walled, larger ventricle. Our data in man were consistent with this theoretical prediction.

Total systolic element work ranged from 127 ± 25 g-cm/cm³ in normal subjects to 38 ± 11 g-cm/cm³ in patients with primary myocardial disease (P <0.001) with t values compared with normal that were the same as for average element power. Values for the relative contribution of the directional components of element work were also the same as for average element power.

As an example of wall element analysis, Figure 5 illustrates the directional components of systole before and after aortic valve replacement in a patient with aortic stenosis. All of the directional components of element power were increased preoperatively, but particularly the radial component associated with wall thickening. Postoperatively, all component values decreased toward normal with that for the radial component showing the greatest reduction. The changes in wall stress, circumferential shortening velocity and wall thickening that explained these alterations in the power components are shown in Figure 6. Preoperatively, the velocity of circumferential shortening (1.1 cm/sec-cm) and wall thickening (2.1 cm/sec-cm) were normal, but left ventricular systolic pressure (230 mm Hg) and equatorial wall stress (473 g/cm²) were elevated above normal with a resulting increase in values of element power. One month after aortic valve replacement, left ventricular systolic pressure was reduced (165 mm Hg) and wall stress was markedly reduced below normal (213 g/cm²). Associated with the reduction in pressure and stress was a marked increase in velocity of circumferential shortening (2.0 cm/sec-cm) and wall thickening (2.9 cm/sec-cm). Twenty-two months postoperatively these variables had returned to normal or near normal values. Changes in the ejection fraction postoperatively paralleled changes in circumference and wall thickness.

Discussion

This study describes the directional components of contraction in relation to wall thickening in the intact heart. In addition to mid-wall circumferential shortening, substantial thickening of the ventricular wall occurred with ejection. There is displacement of blood by wall thickening separate from and in addition to that displaced by inward wall motion due to decreasing circumference. This wall thickening is, in effect, a consequence of myocardial contraction that is expressed in a radial direction and generates components of work and power constituting forty percent of the total generated by a unit element of ventricular wall.

Extent of systolic wall shortening: methods of measurement: The relative importance of these radial components depends upon the measurement of left ventricular wall thickness. The extent of wall thickening during systole, expressed as percent increase over end-diastolic wall thickness, was 45 percent in normal subjects in our study and comparable with that previously reported in man and in animals. For example, Hugenholtz et al.[4] reported systolic wall thickening of 40 percent in 10 patients. Gault et al.[11] found that left ventricular wall thickness increased by 32 percent in six normal patients. Eber et al.[13] measured normal wall thickening of 70 to 197 percent in six normal patients. Lewis and Sandler[29] reported a mean systolic wall thickening of 53 percent in 24 patients (range of 15 to

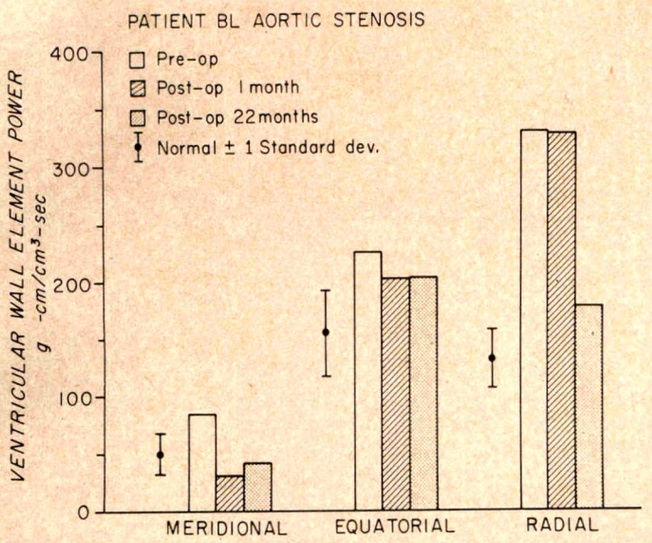

FIGURE 5. Directional components of left ventricular wall element power before and after aortic valve replacement in a patient with aortic stenosis (78 mm Hg gradient). dev. = deviation; Post-op = postoperative; Pre-op = preoperative.

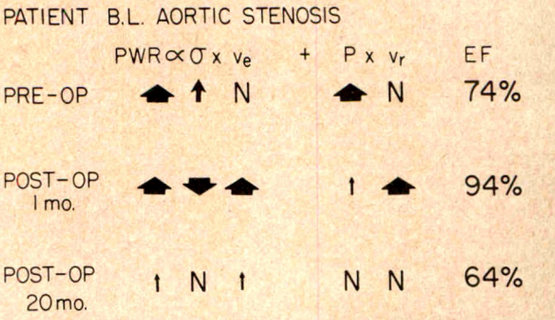

FIGURE 6. Same patient as in Figure 5. Relations of element power (PWR), equatorial wall stress (σ), velocity of circumferential shortening (v_e), ventricular systolic pressure (P), velocity of wall thickening (v_r) and ejection fraction (EF) before (Pre-op) and after (Post-op) aortic valve replacement. The **thick arrows** indicate marked changes from normal values and **thin arrows** indicate smaller deviations from normal. N indicates normal or near normal values.

175 percent depending on the type of heart disease and degree of ventricular impairment). Bunnell et al.[12] described a systolic wall thickening of 58 percent in five normal patients. Dumesnil et al.[14] observed a mean wall thickening of 82 percent (range of 46 to 156 percent) in nine normal subjects. A similar range of normal values has been reported in experimental animals as follows: Heikkila et al.,[8] 32 percent; Bove and Lynch,[30] 43 percent; Leshin et al.,[7] 44 percent; Liedtke et al.,[6] 35 percent; Mitchell et al.,[3] 35 to 45 percent.

However, there is disagreement on the extent of wall thickening in experimental animals. Systolic wall thickening of only 10 to 15 percent has been reported by several groups[9,31–33] using plunge-through measuring devices or endocardial markers. Mitchell et al.[3] provided an explanation for these differences by studying the motion of metallic markers attached to the endocardium in experimental animals. During systole these endocardial markers became buried within the ventricular wall at some distance from the ventricular cavity outlined simultaneously by contrast medium. These observations indicate that two different processes account for total wall thickening during systole as measured directly on angiographic films. The first is anatomic thickening of the wall as the ventricle becomes smaller during contraction due to incompressibility of myocardium. The second process is infolding of the trabeculae carnae during systole, which acts to displace blood from the ventricular cavity. Direct measurements using metallic markers or plunge-through devices attached to the endocardium do not account for or may interfere locally with the infolding of the endocardium that normally results in displacement of blood and development of pressure. On the other hand, direct measurement of systolic wall thickening on angiographic film tends to overestimate wall thickening because of endocardial infolding, which produces a "penumbra" or partially opacified zone around the more dense image of the ventricular cavity on X-ray films. In man, direct measurements of normal systolic wall thickening on angiographic films tend to average greater than 65 percent,[12–14] although two studies yielded notable exceptions of 32[11] and 58 percent, respectively.[29] However, in the latter study the only patients included were those whose ventricular mass calculated from systolic films was comparable with mass calculated from diastolic films, a selection having the same effect as the methods of Hugenholtz et al.[4] and Rackley et al.[5] This problem can be largely overcome by the method developed by the latter authors[4,5] and used in our study in which wall thickness during systole is calculated from end-diastolic wall thickness assuming constant myocardial mass. This method has been validated in man by comparison with postmortem measurements of left ventricular mass[18] and in experimental animals.[19] Thus, although there is conflicting published evidence, our results fall between the overestimates due to measuring wall thickness directly on systolic films and the underestimates due to endocardial markers that may not account for endocardial infolding.

Rate of wall thickening: The normalized rate of wall thickening in our study was 1.81 cm/sec-cm in normal subjects. This value is comparable with the 1.96 lengths/sec reported in experimental animals by Heikkila et al.[8] Dumesnil et al.[14] also measured rate of wall thickening but did not normalize their values for differences in wall thickness or ventricular size. Their results therefore cannot be compared with ours.

Radial components of element work or power: The relative importance of the radial components of element work or power compared with the circumferential components depends not only on ventricular wall thickening but also on where the velocity of circumferential shortening is determined. Velocity of circumferential shortening at the endocardial surface by definition includes the effects of wall thickening, in which case the radial and circumferentaitial components cannot be separately analyzed. However, the ve-

locity of circumferential shortening at mid-wall between the epicardium and endocardium does not include the effects of wall thickening, as proved mathematically in the Appendix. Therefore, in this study mid-wall velocity of circumferential shortening was determined in equatorial and meridional directions to evaluate the relative importance of radial and circumferential components of element work and power.

Clinical importance of components of element power: The equatorial component accounted for 45 percent of total element power in normal subjects and increased to 55 percent ($P < 0.005$) in patients with a severely diseased, dilated ventricle. The radial component of element power due to wall thickening accounted for 40 percent of the total in normal subjects; in contrast to the equatorial component it decreased to 31 percent ($P < 0.001$) in patients with a dilated heart. In patients with aortic stenosis the radial component accounted for 46 percent of total element power, a modest but statistically significant larger percent than in normal subjects ($P < 0.01$). The results indicated that in subjects with a dilated heart the total power and work due to wall thickening was proportionately reduced to a greater extent than total element power. Thus, the relative contribution of the directional components to total element power varied with the type of heart disease as well as its severity.

The meridional component constituted 14 percent of total element power. This proportion was the same in normal subjects as in patients with ventricular dilatation. The small meridional contribution to total element power and work was consistent with previous observations that the left ventricle empties primarily by inward motion of the lateral walls with relatively little change in base to apex dimensions in animals[1,34] and in man.[11,29] In disease states the absolute values of meridional element power were reduced but the relative contribution, or percent of the total, was not significantly decreased. Gault et al.[11] also reported a reduction in the extent of longitudinal shortening in diseased ventricles.

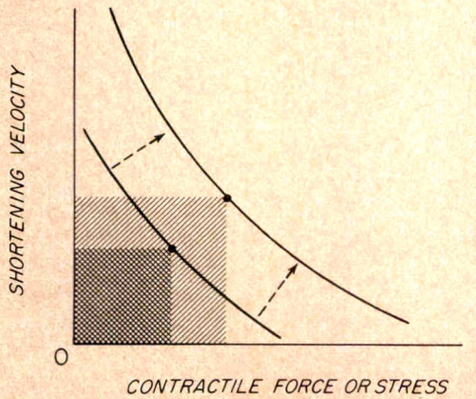

FIGURE 7. Relation of the highest force-velocity curve during a contraction to element power and changes in myocardial "contractility." The **shaded area** indicates graphically the product of force and velocity at a point on the curve. With an increase in contractility, the curve moves upward and rightward as indicated by the **arrows.** Element power then increases as shown by the **larger shaded area.** With a decrease in contractility, the curve moves toward the origin and element power correspondingly decreases (not shown).

Relation to myocardial force-velocity relations: Element power reflects the combined capacity of the myocardium to shorten and to generate force. Levine and Britman[35] have described an inverse linear relation between force developed and the rate of circumferential "fiber" shortening at peak force in the intact heart. Ross et al.[36] have also demonstrated an inverse relation between tension and velocity of shortening at isovolumic points in the canine left ventricle, as well as the shift in this relation with changes in contractility.

A schema illustrating force-velocity relations is shown in Figure 7. As the activation level increases during each systole, the force-velocity relation shifts upward and rightward to the highest curve characterizing that contraction. As the activation level falls during late systole, the force-velocity relation returns toward the origin. An increase in "contractility" is characterized by a further upward and rightward shift of the highest force velocity curve of a contraction. A decrease in contractility is characterized by a downward and leftward shift of the highest curve of a contraction. Peak element power is the product of stress (force) and velocity at any point on the highest force-velocity curve of a contraction, indicated by the shaded area of Figure 7. It increased with a rightward and upward shift in the force-velocity curve and decreased with a leftward and downward shift in the curve. Average element power as presented in this study refers to the average shift of the force-velocity curve during systole. Thus, element power may be viewed in terms of myocardial force-velocity relationships but also provides quantification of the directional components of ventricular function.

Relation to wall stress values: Stress values calculated by the equation of Sandler and Dodge[24] used in this study were 5 to 10 percent higher than the values reported by others.[37–39] Consequently, values of the equatorial or circumferential component of element power were also higher using the Sandler and Dodge equations than they would have been using other stress equations. Values of the radial component of element power were therefore proportionately lower using the stress equations of Sandler and Dodge. Thus, the proportional contribution of radial element power and the relative importance of wall thickening to ventricular function were conservative underestimates in this study. With other stress equations the relative contribution of wall thickening would be even larger than the 40 percent we have reported.

Power and work distribution in ventricle: Values of external pump power divided by ventricular mass did not equal values of unit element power since the latter were specifically in reference to mid-wall elements in equatorial and meridional planes containing the radii of the ventricle. Elements of the wall closer to the apex or base of the heart might not generate the same amount of power and work as at the equator. Since the power and work distribution of elements throughout the whole ventricle was not quantitatively known, total external power and work of the ventricle would not be determined by integrating element equations throughout the wall of the ventricle.

Clinical implications: Wall element analysis permitted quantification of the effects of wall thickening separate from the equatorial and meridional directional contributions to ventricular performance in the intact heart. It also provided sensitive separation of normal and abnormal ventricles. Although analysis of wall element power is complex and, from a practical standpoint, requires computer facilities, it is useful for understanding myocardial performance quantitatively in terms of ventricular geometry and myocardial mechanics in the intact ventricle of patients with valve, coronary and primary myocardial disease.

Acknowledgment

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Control of Cardiac Output in Essential Hypertension

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Cardiac and renal hemodynamics and cardiopulmonary and total blood volume were determined in 202 men, 101 with normotension and 101 of the same age with chronic essential hypertension, normal renal function and balanced sodium intake and urinary output. Cardiac output was identical in the two groups, whereas blood pressure and total peripheral resistance were significantly different. The two groups exhibited strong differences in the correlation study: (1) Correlations of blood pressure with, respectively, heart rate, cardiopulmonary blood volume and total blood volume were significant in the normotensive group but not in the hypertensive group. (2) Correlations of cardiac output with, respectively, heart rate, cardiopulmonary blood volume and total blood volume were significant in both groups. (3) Correlations of renal blood flow with, respectively, cardiac output, blood pressure and total blood volume were significant in the hypertensive group but not in the normotensive group.

This study provides evidence that: (1) the volume and neural control of blood pressure are disrupted in hypertension whereas control of cardiac output is maintained; and (2) adaptive mechanisms involving renal function are necessary to the maintenance of normal cardiac output in patients with essential hypertension.

Since total peripheral resistance has not been directly measured, the respective roles of cardiac output and resistance in the mechanism of hypertension have remained controversial. In most types of hypertension, total peripheral resistance is greatly increased whereas cardiac output is nearly normal. These findings have usually been thought to indicate that hypertension is caused by some primary factor that increases resistance without changing cardiac output. More recently, on the basis of animal experiments and computer analysis,[1–3] it has been shown that a primary increase in cardiac output can cause increased total peripheral resistance and therefore increased blood pressure. This theory assumes that the maintenance of a normal cardiac output in established hypertension requires important adaptive mechanisms in the systemic circulation.[4]

That regulation of arterial pressure is an essential ingredient in regulation of cardiac output is easy to demonstrate in animal experiments in which precise time-dependent relations of hemodynamic variables can be determined and compared. However, such data are difficult to establish in man. Clinical hemodynamic studies are performed either in the steady state or in unstable conditions involving only short-term control of blood pressure. Therefore, the mechanism of the normal cardiac output in essential hypertension is still unknown. The purpose of this study was to investigate the adaptive mechanisms that explain (or are related to) the normal cardiac output in patients with chronic essential hypertension.

This work was performed by the Hemodynamic Laboratory (Prof. Ag. Safar) of the Hypertension Research Center, Department of Prof. Milliez, Hospital Broussais, Paris and U.E.R. Saint-Quentin (Prof. Chau), Université de Picardie, France. This study was supported by a grant-in-aid from the Institut de la Santé et de la Recherche Médicale (INSERM), Paris, France, the Association pour l'Utilisation du Rein Artificiel (AURA), Paris, France; and the Délégation Générale à la Recherche Scientifique et Technique (DGRST), Paris, France. Manuscript received December 29, 1975, accepted February 18, 1976.

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Material and Methods

Selection of subjects: The study group was composed of 202 men, 101 with normal blood pressure and 101 with hypertension. All subjects were 20 to 40 years old (mean ±1 standard error of the mean 28.5 ± 1 years). The patients were untreated or had discontinued treatment at least 4 weeks before the study. They were hospitalized for 6 days and given a 110 mEq/day sodium diet. During hospitalization, on the basis of weight, sodium intake and urinary output, sodium balance was considered to be in the steady state. Extensive investigations included determination of serum and urinary electrolytes, catecholamines and endogenous creatinine clearance levels and timed intravenous urography with wash-out test or renal arteriography, or both. The 101 hypertensive patients were diagnosed as having essential hypertension. None had renal, cardiac or neurologic involvement. The mean endogenous creatinine clearance of the overall population was 97 ± 3 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$. The protocols were approved by INSERM (Institut National de la Santé et de la Recherche Médicale). Informed consent was obtained from the patients after a detailed description of the procedure.

Hemodynamic determinations: On the 3rd hospital day, hemodynamic studies were performed after the patients had fasted overnight. No premedication was administered. Under local procaine anesthesia, polyethylene catheters were in-

TABLE I

Hemodynamic Characteristics of the Two Groups (mean ± standard error of the mean)

Variable	Normotensive Group (101 patients)	Hypertensive Group (101 patients)
Age (yr)	28 ± 1	29 ± 1
Weight (kg)	71 ± 1	75 ± 1**
Height (cm)	172 ± 1	174 ± 1
SAP (mm Hg)	138 ± 2	176 ± 3***
DAP (mm Hg)	76 ± 1	107 ± 2***
MAP (mm Hg)	97 ± 2	132 ± 2***
HR (beats/min)	76 ± 1	77 ± 1
CO		
(ml/min)	7173 ± 165	7166 ± 157
(ml/kg)	103 ± 2	97 ± 3
SV (ml/kg)	1.4 ± 0.03	1.3 ± 0.02
TPR (arbitrary unit · kg)	990 ± 23	1453 ± 44***
TBV		
(ml)	5245 ± 132	5355 ± 127
(ml/kg)	75 ± 1	72 ± 1**

** = $P < 0.01$; *** = $P < 0.001$ (in comparison with values in normotensive group).

CO = cardiac output; DAP = diastolic arterial pressure; HR = heart rate; MAP = mean arterial pressure; SAP = systolic arterial pressure; SV = stroke volume; TBV = total blood volume; TPR = total peripheral resistance.

	Age	Weight	Height	SAP	DAP	MAP	HR	CO	SV	TPR	TBV
Age		0.03 0.20	-0.19 -0.19	0.00 0.44	0.11 0.38	0.10 0.45	-0.14 -0.09	-0.19 -0.37	-0.06 -0.32	0.25 0.51	0.07 -0.17
Weight	0.03 0.20		0.50 0.42	0.19 0.11	0.17 0.00	0.19 0.05	-0.08 -0.00	-0.39 -0.30	-0.40 -0.33	0.49 0.26	-0.61 -0.33
Height	-0.19 -0.19	0.50 0.42		0.14 -0.02	0.11 -0.16	0.14 -0.12	-0.06 0.01	-0.15 0.16	-0.12 0.14	0.22 -0.23	-0.18 0.10
SAP	0.00 0.44	0.19 0.11	0.14 -0.02		0.63 0.82	0.83 0.93	0.23 0.09	0.21 -0.03	0.02 -0.10	0.22 0.52	-0.22 0.04
DAP	0.11 0.38	0.17 0.00	0.11 -0.16	0.63 0.82		0.92 0.95	0.32 0.11	0.02 -0.09	-0.18 -0.18	0.45 0.58	-0.33 0.06
MAP	0.10 0.45	0.19 0.05	0.14 -0.12	0.83 0.93	0.92 0.95		0.29 0.10	0.09 -0.06	-0.16 -0.15	0.41 0.58	-0.29 0.06
HR	-0.14 -0.09	-0.08 -0.00	-0.06 0.01	0.23 0.09	0.32 0.11	0.29 0.10		0.51 0.34	-0.32 -0.34	-0.28 -0.18	-0.02 -0.06
CO	-0.17 -0.26	0.28 0.29	0.18 0.44	0.36 0.01	0.15 -0.10	0.24 -0.05	0.47 0.33		0.63 0.74	-0.83 -0.80	0.30 0.39
SV	-0.06 -0.21	0.36 0.30	0.27 0.41	0.19 -0.06	-0.12 -0.20	0.01 -0.14	-0.35 -0.37	0.65 0.73		-0.46 -0.27	0.37 0.39
TPR	0.24 0.44	-0.17 -0.19	-0.11 -0.41	0.14 0.48	0.40 0.59	0.35 0.57	-0.26 -0.20	-0.79 -0.81	-0.68 -0.66		-0.46 -0.27
TBV	0.12 0.06	0.40 0.67	0.33 0.47	-0.04 0.12	-0.17 0.04	-0.12 0.08	-0.11 -0.06	0.19 0.40	0.31 0.41	-0.28 -0.27	

NORMALIZED DATA (Weight)

UNNORMALIZED DATA

0.03 ← NORMOTENSIVE GROUP (n = 101)
0.20 ← HYPERTENSIVE GROUP (n = 101)

r	p
0.19	< 0.05
0.25	< 0.01
0.32	< 0.001

The correlation exists in the normotensive group but not in the hypertensive group.

The correlation exists in the hypertensive group but not in the normotensive group.

The correlation exists in both groups.

FIGURE 1. Correlation coefficients (*r* values) in the two groups. The *r* values are presented with both unnormalized and weight-normalized data (see Appendix). CO = cardiac output; DAP = diastolic arterial pressure; HR = heart rate; MAP = mean arterial pressure; SAP = systolic arterial pressure; SV = stroke volume; TBV = total blood volume; TPR = total peripheral resistance.

TABLE II

Correlations Between Cardiopulmonary Blood Volume and Renal Blood Flow With Other Variables in the Two Populations

	Cardiopulmonary Blood Volume (ml/kg)		Renal Blood Flow (ml/min per kg)	
Correlations With	Normotensive Group (no. = 28) (mean value ± SEM: 14 ± 1)	Hypertensive Group (no. = 33) (mean value ± SEM: 15 ± 1)	Normotensive Group (no. = 31) (mean value ± SEM: 26 ± 1)	Hypertensive Group (no. = 48) (mean value ± SEM: 24 ± 1)
Age	0.07	−0.20	0.07	−0.33*
Weight	−0.33	−0.15	−0.02	−0.15
Height	−0.18	0.16	0.00	0.20
SAP	0.42*	−0.26	−0.23	−0.24
DAP	0.49**	−0.35*	−0.04	−0.41**
MAP	0.48**	−0.35*	−0.10	−0.37**
HR	0.15	0.06	0.12	0.06
CO	0.61***	0.54**	−0.11	0.50***
SV	0.59**	0.40*	−0.20	0.32*
TPR	−0.42*	−0.54**	0.03	−0.56***
TBV	0.32	0.32	0.00	0.39**

* $P < 0.005$; ** $P < 0.01$; *** $P < 0.001$ in comparison with values in the normotensive group. Abbreviations as in Table I.
SEM = standard error of the mean; other abbreviations as in Table I.

troduced into the right brachial artery and median antecubital vein and under fluoroscopic control were advanced, respectively, into the aortic arch and the main pulmonary artery. The arterial catheter was then placed in the aortic root immediately distal to the aortic valves for intraarterial pressure measurements, and blood pressure, cardiac output and cardiopulmonary blood volume were measured as previously described elsewhere.[5] Total peripheral resistance (TPR) was calculated according to the formula: TPR (arbitrary unit) = MAP/CO × 1,000, where MAP is the mean arterial pressure and CO is cardiac output. Cardiopulmonary blood volume (CPBV) was expressed as the volume between the main pulmonary artery (PA) and the tip of the arterial catheter(Ar). It was calculated as follows: CPBV = CO × TTM, TTM being the mean transit time in seconds between the pulmonary artery and the catheter tip.[6] Total blood volume was measured before the hemodynamic study by the isotope dilution method, using radioiodinated albumin as previously described.[5,6] Renal blood flow was estimated with the iodine-131 hippuran clearance technique and determined with use of the single injection method and the one compartment mamillary system model.[7] Normalization of weight was used to express blood flow, blood volume and stroke volume (see Appendix).

Classification of patients: The main purpose of the study was to investigate control of cardiac output at different levels of blood pressure. Therefore, patients were classified into two groups according to the level of blood pressure measured during the hemodynamic study on the 3rd hospital day. In the normotensive group (101 patients), diastolic blood pressure was 90 mm Hg or less and systolic pressure was 160 mm Hg or less. In the hypertensive group (101 patients), diastolic pressure was more than 90 mm Hg.

Table I lists the main characteristics of the two groups. Age and cardiac output were identical in both groups; blood pressure and total peripheral resistance were significantly different.

Statistical studies: Statistical calculations[8] were performed for three purposes: (1) To point out the significant correlations between the main hemodynamic variables in the normotensive and hypertensive groups; (2) To compare the correlations between two given variables. The following three results were observed: (a) the correlation was significant in one group, but not in the other; (b) the correlation was significant in both groups, but at different levels; and (c) the correlation was significant in both groups, at the same level. In the latter case, a regression analysis ($Y = aX + b$) was performed, and the values of a and b in the two groups were compared. (3) To interpret the results by constructing a systematic presentation of factors that interfere directly or indirectly in the regulation of cardiac output. Some differences between the two groups were interpreted as an adaptive mechanism possibly related to the maintenance of a normal cardiac output in the hypertensive patients.

Results

Normalization for body weight was used in Figure 1 and Tables I (right column) to III.

Correlation coefficients (Figure 1 and Table II): The results in Figure 1 can be summarized as follows. By comparison with findings in the normotensive group, the following occurred in the hypertensive group:

1. These correlations were disrupted: (a) blood pressure (systolic, mean) with body weight; (b) blood pressure (systolic, diastolic, mean) with heart rate; (c) blood pressure (systolic) with cardiac output; (d) blood pressure (systolic, diastolic, mean) with blood volume; and (e) total peripheral resistance with heart rate. Table II showed similar results concerning the correlation between blood pressure and cardiopulmonary blood volume.

2. These correlations appeared in the hypertensive group: (a) age with several hemodynamic variables (blood pressure and cardiac output, among others).

3. These correlations were maintained: (a) cardiac output (or stroke volume) with blood volume (or body weight); (b) cardiac output (or stroke volume) with heart rate; and (c) total peripheral resistance with blood volume.

Table II summarizes the data on renal blood flow. In the normotensive group, there was no correlation between renal blood flow and the other hemodynamic variables. In contrast, in the hypertensive group, renal blood flow was correlated (1) negatively with blood pressure, and (2) positively with cardiac output and blood volume.

Regression coefficients (Table III): To get further information on the correlations that were significant in both groups, a regression analysis was made. Table III shows that the regression coefficients of cardiac output versus weight, heart rate and blood volume were similar in the two groups. In contrast, from the normotensive to the hypertensive group, the volume-resistance regression curve had two characteristics: (1) it was reset to the right, and (2) the slope was significantly more shallow.

Comments

Despite the large differences in blood pressure levels, the normotensive and hypertensive groups had the same cardiac output. These were striking differences in the correlations between hemodynamic variables: (1) Correlations with age existed in the hypertensive group but not in the normotensive group; (2) correlations with blood pressure existed in the normotensive group but not in the hypertensive group; and (3) correlations with cardiac output were maintained in both groups. Age is a well known factor in hypertension. Therefore, points (2) and (3) are the main subjects of our comments.

Control of cardiac output in the normotensive group: As shown in Figure 2, the correlations of cardiac output with heart rate, cardiopulmonary and total blood volume are indications of neural and volume control of cardiac output.[9] However, our study points to subtle interrelations between cardiac output and blood pressure in normal conditions.

Sympathetic activity interferes with regulation of both blood pressure and cardiac output, as demonstrated by the previously described correlation between heart rate and blood pressure.[10] Additional evidence was provided in this study by the direct correlation between cardiopulmonary blood volume and blood pressure. More important is the volume control, which has been studied by the pressure-volume (or resistance-volume) relation.[11] This correlation demonstrates the existence of a volume-pressure adaptive mechanism.[7] When blood pressure increases, volume decreases, and this factor contributes to maintenance of pressure within normal ranges. Such results reflect the long-term pressure-body fluid control mechanism described by Guyton and Coleman.[3] The increase in pressure causes the kidney to excrete more water and salt, thus decreasing blood volume, cardiac output and, in turn, total peripheral resistance, and finally causing a decrease in pressure level.

Disrupted relations in the hypertensive group (Fig. 2): The correlations between volume and neural control of cardiac output were maintained in the hypertensive group. In contrast, the interrelations between cardiac output and blood pressure were disrupted. No correlation existed between heart rate and blood pressure. In addition, the correlation between blood pressure

TABLE III

Regression Data in the Two Groups

Y	X	Group	*r* Value	a Value ± Standard Error up to 5%†	b Value ± Standard Error up to 5%†
CO	Weight	N	−0.39	−0.81 ± 0.38	160 ± 27
		H	−0.34	−0.75 ± 0.42	153 ± 31
CO	HR	N	0.51	0.87 ± 0.29	36 ± 22
		H	0.34	0.63 ± 0.34	48 ± 27
CO	TBV	N	0.30	0.57 ± 0.35	60 ± 27
		H	0.39	1.07 ± 0.51	20 ± 37
TBV	TPR	N	0.46	−0.02 ± 0.008	97 ± 9
		H	0.27	−0.005 ± 0.004*	80 ± 6

* $P < 0.05$.
† According to Student's table.
H = hypertensive group (no. = 101); N = normotensive group (no. = 101); Y = aX + b regression line; other abbreviations as in Table I.

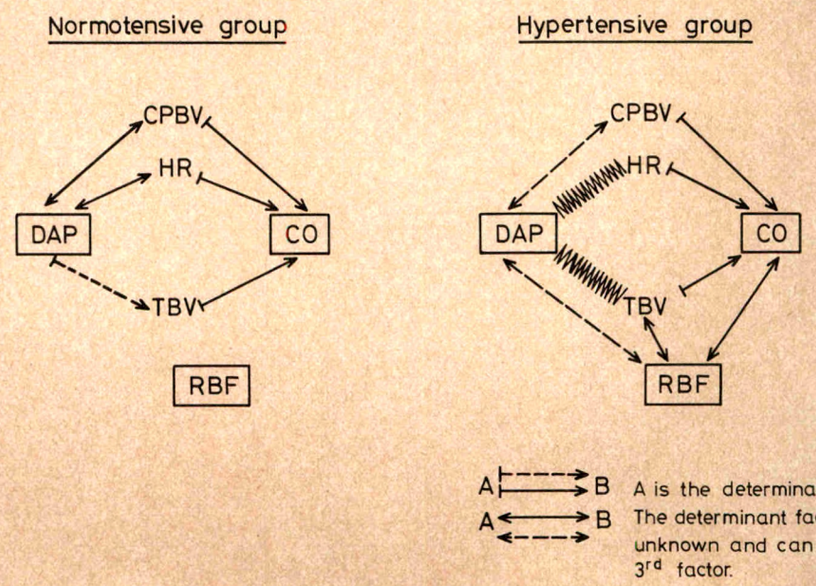

FIGURE 2. Control of cardiac output in the normotensive and hypertensive groups. CO = cardiac output; CPBV = cardiopulmonary blood volume; DAP = diastolic arterial pressure; HR = heart rate; RBF = renal blood flow; TBV = total blood volume. **Solid line** indicates a positive correlation; **dashed line** a negative correlation; **wavy line** a disrupted correlation.

and cardiopulmonary blood volume was negative. These observations agree with the reduced neurogenic activity previously emphasized in chronic essential hypertension.[12]

The most significant finding was the loss of the pressure (or resistance)-volume relation that contributed to the control of cardiac output in the normotensive group. The volume-resistance relation of hypertensive patients had two characteristics: (1) The curve was reset, so that, at each level of resistance, the blood volume was greater in hypertensive than in normotensive subjects; and (2) the slope was significantly decreased, indicating a reduced ability of the system to decrease the volume per unit of rise in resistance. Such a curve was described in patients with a steady state sodium balance. Therefore, the blood volume was sufficient to maintain the steady state of sodium balance and the normal cardiac output, but was too great to allow the pressure to return to normal values. The maintenance of such blood volume implied the existence of an underlying renal mechanism.[13]

Control of cardiac output in the hypertensive group (Fig. 2): That a renal mechanism is involved in the maintenance of the cardiac output level in hypertensive patients was demonstrated by the renal blood flow correlation study. In the normotensive group, renal blood flow was not correlated with any hemodynamic variable. This finding was in agreement with the classic concept of autoregulation of blood flow in the normal renal circulation. In contrast, hypertensive patients had direct correlations of renal blood flow with blood volume and cardiac output. These observations point to the loss of the blood flow autoregulation and, consequently, to a renal defect. The negative correlation between blood pressure and renal blood flow does not contradict this concept. Tobian et al.[14] have demonstrated that lack of autoregulation is essential to provide a normal rate of flow in hypertensive kidneys perfused at elevated levels of pressure.

In conclusion, our study points to the role of a functional renal abnormality in the maintenance of the normal cardiac output level in patients with essential hypertension.

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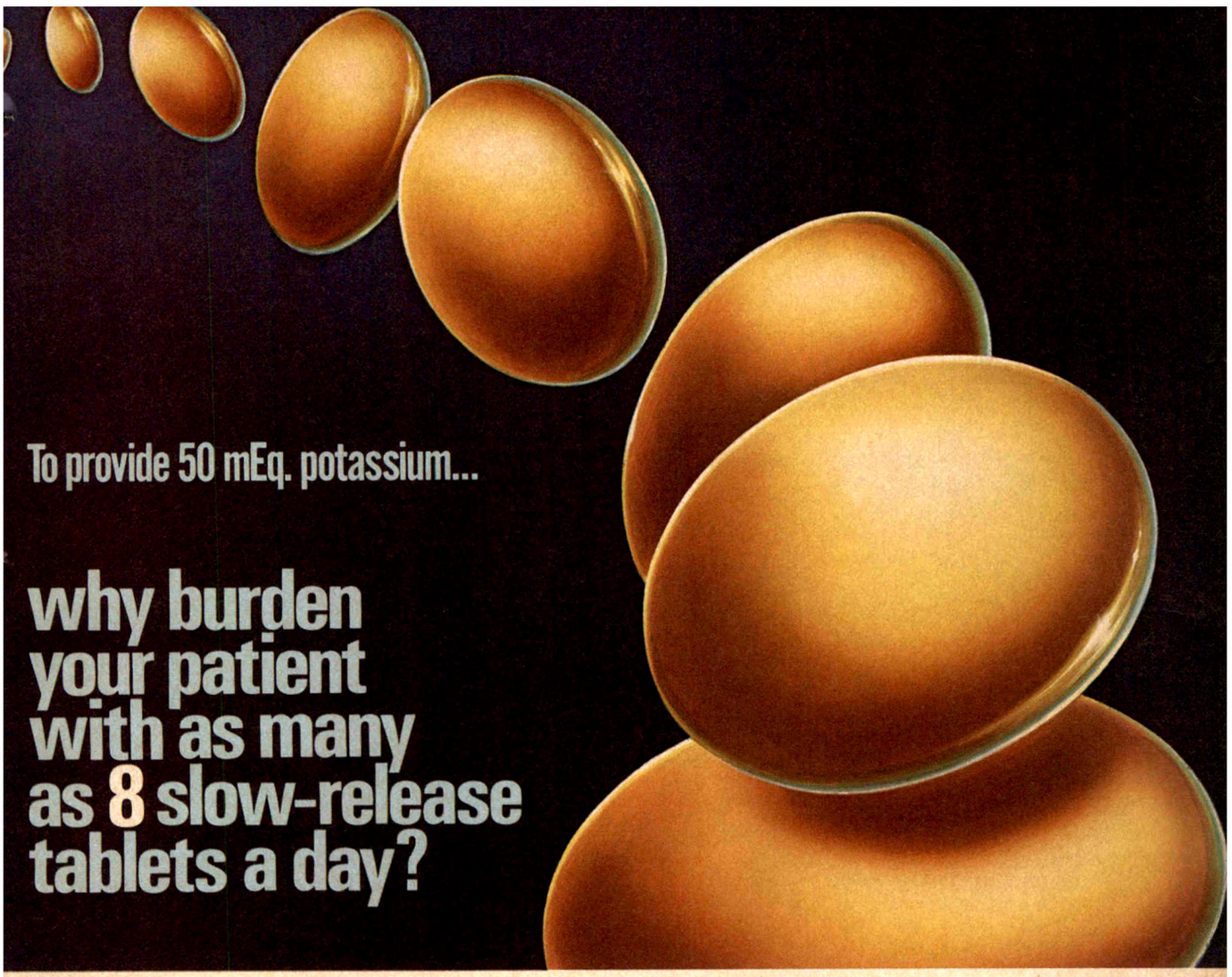
APPENDIX

The correlation coefficients (r values) could depend on the normalization procedure. Figure 1 summarizes the results determined by using either unnormalized or weight-normalized data. This figure suggests two comments:

Comparison between unnormalized and weight-normalized data: In both cases, the r values were similar, except for the pressure-volume relation; the correlation existed only for normalized blood volume. This finding could be explained by the strong correlation between unnormalized blood volume and body weight. The negative pressure-volume relation became obvious only after elimination of the role of body weight. The pressure-volume relation existed also when data were normalized for body height.[11]

Comparison between weight normalization and other types of normalization: Normalization for body weight, body surface area and height yielded similar r values. In addition, Figure 1 allowed an indirect comparison between the weight and the height normalization data: (1) The correlations of height with the unnormalized hemodynamic data (cardiac output, blood volume) were not observed after normalization for weight, and (2) several correlations such as the unnormalized blood volume-cardiac output correlation existed even with a constant weight, but not with a constant height (partial correlation coefficient study). These results reflected the strong weight-height correlation and justified the normalization for weight.



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Indications: K-Lyte is an oral potassium supplement for therapy or prophylaxis of potassium deficiency. It is particularly useful when thiazide diuretics, corticosteroids, or severe vomiting and diarrhea cause excessive excretory potassium losses; and when dietary potassium is low. Carefully monitored, it may also be useful for potassium replacement where digitalis intoxication results in cardiac arrhythmias.

Contraindications: Impaired renal function with oliguria or azotemia; Addison's disease, hyperkalemia from any cause.

Warnings and Precautions: Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be administered with caution, and dosages adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal kidney function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Frequent checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also be directed toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients and such patients should be monitored by ECG for cardiac irregularities. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, **patients should be carefully directed to dissolve each dose completely in the stated amount of water.**

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts.

Dosage and Administration: Adults: 1 tablet (25 mEq. potassium) completely dissolved in **3 to 4 ounces of cold or ice water,** 2 to 4 times daily, depending upon the requirements of the patient. The normal adult daily requirement is approximately 50 mEq. of elemental potassium. NOTE: **It is suggested that this product be taken with meals and sipped slowly over a 5-10 minute period.**

How Supplied: K-Lyte effervescent tablets (orange or lime flavors) cartons of 30 and 250.

Mead Johnson LABORATORIES

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First in Company Size

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The Siemens Company is the largest electro-medical company in the world. When the concept of implanting a pacemaker first evolved, we were able to assign a team of experienced medical electronic scientists to work on its development.

Since the first pacemaker (Siemens-Elema Fixed Rate Model) was implanted in 1958, our company has developed the most complete line of pacemakers in the world. Over 60,000 Siemens-Elema pacemakers have been implanted to date.

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In Sweden, 1958, Drs. Åke Senning and R. Elmqwist introduced the first implantable pacemaker—a product developed by Siemens-Elema. Since then over 60,000 successful Siemens-Elema implants have been made. Our early and continuous pacemaker research has placed us in a unique position of technological leadership.

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Since development of the first pacemaker and the unique Elema electrode, we have tested all new concepts repeatedly before introduction. As a result, Siemens-Elema is the only major pacemaker producer who has had no recalls since 1967.

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- ☐ QRS-inhibited lithium pacemaker Model 207 (1.0 ms impulse)
- ☐ QRS-inhibited lithium pacemaker Model 217 (0.5 ms impulse)
- ☐ QRS-inhibited lithium pacemaker Model 187 (0.75 ms impulse)
- ☐ QRS-inhibited Variopacemaker* Model 159 (1.0 ms impulse)
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  *With patient threshold value measuring feature
- ☐ QRS-inhibited pacemaker Model 157 (1.0 ms impulse)
- ☐ QRS-inhibited pacemaker Model 177 (0.5 ms impulse)
- ☐ QRS-synchronous pacemaker Model 153E (1.0 ms impulse)
- ☐ Fixed-rate pacemaker Model 152C (1.0 ms impulse)
- ☐ Atrial-triggered pacemaker Model 155/156**

  **Model 156 has more sensitive P-wave amplifier
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- ☐ Our Unique Balloon Lead
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A51

SIEMENS-ELEMA

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5-6 Years Usable Life-Smaller Size.

Lithium

USABLE LIFE—5-6 YEARS

THICKNESS—5/8" 17 mm

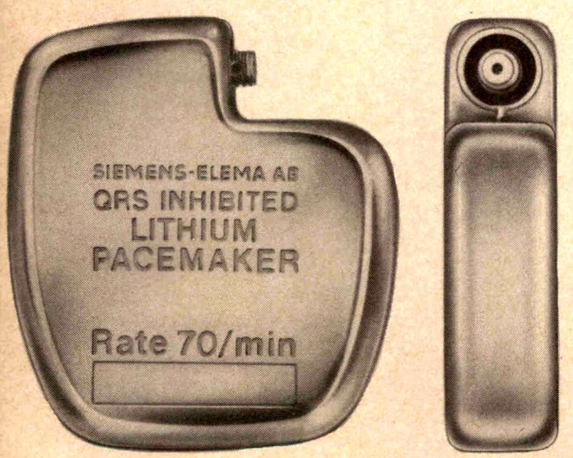
WEIGHT—100g

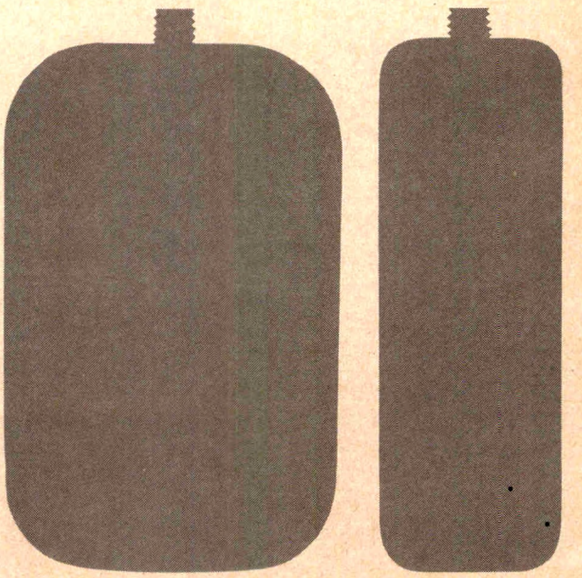
Mercury

USABLE LIFE—3 YEARS

THICKNESS—1" 25 mm

WEIGHT—155g





Advantages:

Siemens was one of the first to develop a lithium powered pacemaker with double the usable life of mercury models. While not the first to market one, our additional testing and research has produced a group of lithium pacemakers with significant advantages.

The smooth, rounded contour and slender profile has proved very comfortable for the patient.

The basic rate of 70 impulses per minute is maintained throughout the life of the pacemaker. The basic rate is not dependent upon battery voltage and thus it does not decline during its useful lifetime.

Two distinct cell depletion indicators are offered only in Siemens-Elema lithium pacemakers. A magnet test rate drops from 100 impulses per minute to 85 per minute indicating aging. A drop in basic rate from 70 to 60 impulses per minute makes the patient aware of need for replacement prior to a 3-month safety period. These tests are especially important in pacemakers with 5 to 12 years usable life.

QRS-inhibited Model 207 has an impulse duration of 1.0 ms and Model 217 has an impulse duration of 0.5 ms. While somewhat more expensive than mercury pacemakers, the cost per year of usable life is 25-30% less. These two 6-year lithium pacemakers are 33% thinner and lighter than mercury models offering 3 years usable life. Patient comfort is increased, incidence of irritation and perforation is significantly reduced.

Our Model 187 lithium pacemaker (.75 ms impulse duration) offers up to 12 years usable life. This model also is only ⅝" (17 mm) thick, while overall volume and weight is similar to a 3 year mercury pacemaker.

Other Features:

Stable electrical parameters throughout the pacemaker's life. Practically insensitive to interference. For extra safety, the pacemaker switches from the inhibited mode in the event of unusually strong fields of interference.

Defibrillation-proof.

Run-away protection.

Pacemaker housing is hermetically-sealed titanium; the lithium-iodide cell is also hermetically sealed for greatest reliability. Pulse amplitude decreases only 0.8V from beginning to end of estimated pacemaker life.

CALL COLLECT FOR A LITHIUM PACEMAKER DEMONSTRATION OR WRITE FOR LITERATURE.

☐ Please call for an appointment to demonstrate Siemens-Elema lithium pacemakers.
☐ Please send literature describing Models 187, 207 and 217.

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A53

Lidov

When choosing a diuretic for day-in-day-out hypertension control with comfortable compliance...

The problem of maintaining antihypertensive control rises anew with each dawn.

That is why the agent you choose in mild to moderate essential hypertension should offer (1) long-term effectiveness, (2) patient comfort and compliance.

Zaroxolyn offers both.

In one long-term study[1] Zaroxolyn brought moderately elevated (average 161/109 mm Hg) blood pressure down to the range of normotension—and held it there for a year or more.

The investigator noted, "Patient cooperation was surprisingly good for a study of such duration [2½ years]. The once-daily dosage schedule with metolazone [Zaroxolyn] no doubt contributed to patient compliance."

And overall patient compliance with Zaroxolyn is good—very good. An analysis of controlled clinical studies involving 188 Zaroxolyn patients showed that only eight discontinued therapy because of side effects. That's a discontinuation rate of only 4.3%. Broader clinical experience appears to substantiate this low rate of discontinuance[2]

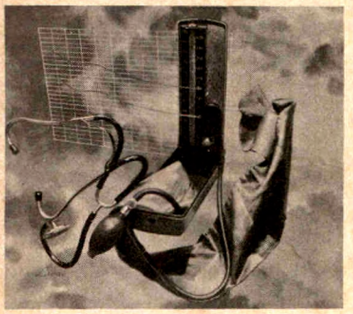
Zaroxolyn. For long-term control and comfortable compliance in mild to moderate essential hypertension.

Zaroxolyn® (metolazone, Pennwalt)
2½-mg, 5-mg and 10-mg tablets

once-daily antihypertensive-diuretic

Please see next page for prescribing information.

Zaroxolyn® (metolazone, Pennwalt)
Effective, comfortable, long-acting antihypertensive therapy from a single daily dose.



2½ mg 5 mg 10 mg

Recommended Dosages Zaroxolyn® (metolazone)	
Mild to moderate essential hypertension	2½ to 5 mg once daily
Edema of cardiac failure	5 to 10 mg once daily
Edema of renal disease	5 to 20 mg once daily

NOTE: The daily dosage depends on the severity of each patient's condition, his sodium intake, and his responsiveness. Therefore, dosage adjustment is usually necessary during the course of therapy.

Prescribing Information

INDICATIONS: ZAROXOLYN (Metolazone) is indicated for the treatment of edema accompanying congestive heart failure and renal disease, and to reduce blood pressure in the management of mild to moderate essential hypertension.

CONTRAINDICATIONS: Anuria, Hepatic coma or pre-coma; Allergy or hypersensitivity to ZAROXOLYN.

The routine use of diuretics in an otherwise healthy pregnant woman, with or without mild edema, is contraindicated and possibly hazardous.

WARNINGS: While not reported to date, cross-allergy theoretically may occur when ZAROXOLYN is given to patients known to be allergic to sulfonamide-derived drugs, thiazides, or quinethazone.

Hypokalemia may occur, with consequent weakness, cramps, and cardiac dysrhythmias. It is a particular hazard in digitalized patients; dangerous or fatal arrhythmias may be precipitated.

Azotemia and hyperuricemia may be noted or precipitated during the administration of ZAROXOLYN. Infrequently, gouty attacks have been reported in persons with history of gout. Discontinue ZAROXOLYN if azotemia and oliguria worsen during treatment of patients with severe renal disease.

Presently, ZAROXOLYN is not recommended for pediatric patients.

ZAROXOLYN will, on occasion, exhibit considerable potentiation when administered concurrently with furosemide. Excessive, massive volume and electrolyte depletion may result. Exert care, especially during initial therapy, when using ZAROXOLYN with other antihypertensives. Dosage of other antihypertensive agents, especially the ganglionic blockers, should be reduced.

Use of ZAROXOLYN with a potassium-sparing diuretic may potentiate diuresis; dosage should be reduced. Potassium retention and hyperkalemia may result; serum potassium should be determined frequently. Potassium supplementation is contraindicated when a potassium-sparing diuretic is given.

USAGE IN PREGNANCY (See Contraindications): Since ZAROXOLYN crosses the placenta, and appears in the cord blood, its administration to women of child bearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. The potential effects on the fetus include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

NURSING MOTHERS: ZAROXOLYN appears in breast milk. Thus it is possible that the effects of ZAROXOLYN may occur in the newborn. If the use of ZAROXOLYN is deemed essential for a nursing mother, the patient should stop nursing.

PRECAUTIONS: Periodic assessment of serum electrolytes, blood urea nitrogen, uric acid, and glucose levels should be made at intervals during therapy.

Patients receiving ZAROXOLYN therapy should be observed for clinical signs of fluid and/or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Serum potassium should be determined regularly, and potassium supplementation instituted as indicated. Hypokalemia will be more common in association with intensive or prolonged diuretic therapy, with concomitant steroid or ACTH therapy, and with inadequate electrolyte intake.

While not reported to date for ZAROXOLYN, related diuretics have increased responsiveness to tubocurarine and decreased arterial responsiveness to norepinephrine. Accordingly, it may be advisable to discontinue ZAROXOLYN three days before elective surgery.

Observe caution when administering ZAROXOLYN to hyperuricemic or gouty patients. ZAROXOLYN exerts minimal affects on glucose metabolism; insulin requirements may be affected in diabetics, and hyperglycemia and glycosuria may occur in patients with latent diabetes.

Chloride deficit and hypochloremic alkalosis may occur. In patients with severe edema accompanying cardiac failure or renal disease, a low-salt syndrome may be produced; hot weather and a low-salt diet will contribute.

Observe caution when administering ZAROXOLYN to patients with severely impaired renal function. As most of the drug is excreted by the renal route, cumulative effects may be seen in this circumstance.

Orthostatic hypotension may occur; this may be potentiated by alcohol, barbiturates, narcotics, or concurrent therapy with other antihypertensive drugs.

While not reported for ZAROXOLYN, use of other diuretics has been associated on rare occasions with pathological changes in the parathyroid glands, with hypercalcemia and hypophosphatemia.

ADVERSE REACTIONS: *Gastrointestinal reactions:* Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis. *Central nervous system reactions:* syncope, dizziness, drowsiness, vertigo, headache. *Cardiovascular reactions:* orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation and chest pain. *Hematologic:* leukopenia, *Dermatologic-hypersensitivity:* urticaria and other skin rashes. *Other reactions:* dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine; fatigue, muscle cramps or spasm, weakness, restlessness, chills and acute gouty attacks.

Adverse reactions which occur with other diuretics, but have not been reported to date for ZAROXOLYN include: pancreatitis, paresthesias, xanthopsia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity and necrotizing angiitis (cutaneous vasculitis). These reactions should be considered as possible occurrences with clinical usage of ZAROXOLYN.

Whenever adverse reactions are moderate or severe, dosage should be reduced or therapy withdrawn.

HOW SUPPLIED: Tablets, 2½, 5 and 10 mg.

References:

1. Dornfeld L, Kane R: Metolazone in essential hypertension. The long-term clinical efficacy of a new diuretic. *Curr Ther Res* **18:** 527-533, 1975.
2. Data on file, Medical Department, Pennwalt Prescription Products.

PENNWALT

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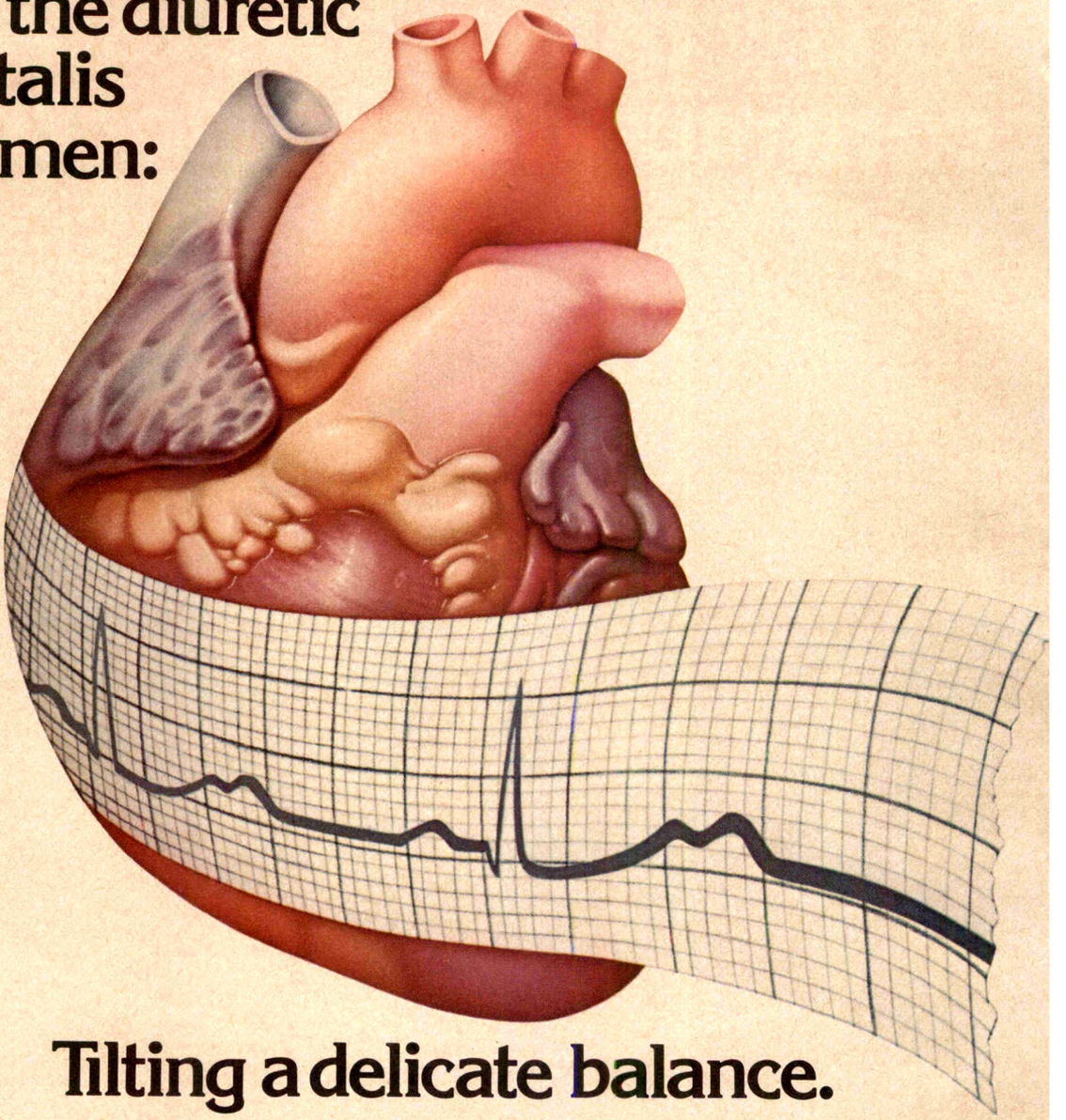
Hypokalemia and the diuretic digitalis regimen:



Tilting a delicate balance.

Certain diuretics such as thiazides, furosemide, and ethacrynic acid may remove potassium and the resulting potassium deficit can rapidly trigger arrhythmias in the digitalized patient. Of course, potassium supplements should not be administered with any potassium-sparing diuretics such as spironolactone and triamterene.

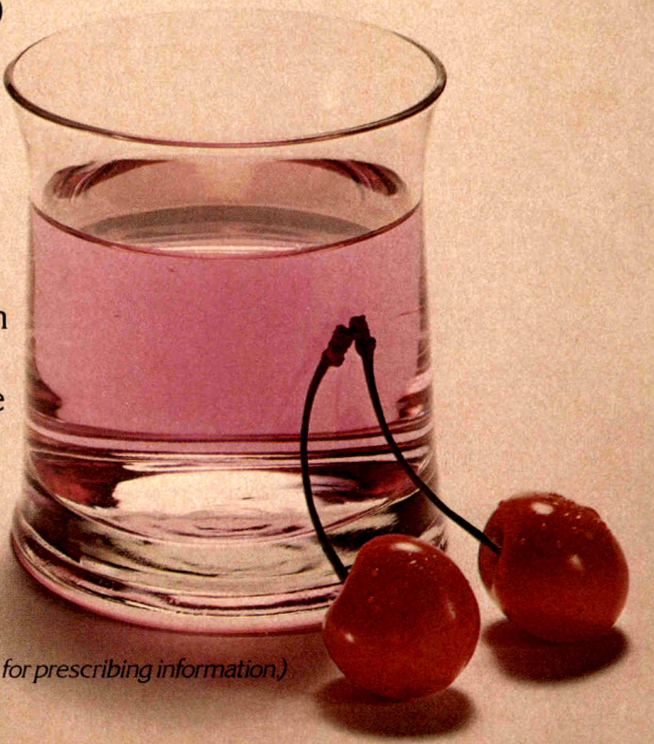
NOW
Kaon-CL 20%™
(potassium chloride)

Offers an economical, convenient therapeutic dose to correct hypokalemia or treat mild digitalis intoxication.

CONVENIENT, ECONOMICAL DOSAGE

■ One tablespoon (15 ml.) provides 40 mEq. each of potassium and chloride...nearly twice the potassium content of most single effervescent tablets or packets of powder.

■ Pleasant Cherry Flavor: One tablespoon (15 ml.) mixed with six fluid ounces of water or other liquid, few palatability problems are encountered. Kaon-CL 20% must be diluted before administration to avoid gastrointestinal irritation.



(See brief summary on following page for prescribing information.)

WARREN-TEED
PHARMACEUTICALS INCORPORATED
SUBSIDIARY OF ROHM AND HAAS COMPANY
COLUMBUS, OHIO 43215

Kaon-CL 20%™ (potassium chloride) Sugar-Free.
Description: Each 15 ml (tablespoonful) supplies 40 mEq each of potassium and chloride (as potassium chloride, 3 g) with saccharin and flavoring. Alcohol 5%.
Indications: Kaon-CL 20% is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. Kaon-CL 20% is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.
Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).
Warnings: Do not administer full strength. Kaon-CL 20% will cause gastrointestinal irritation if administered undiluted. For details regarding adequate dilution, see Dosage and Administration.

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation.

Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.
Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.
Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).
Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.
Dosage and Administration: Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.

One tablespoonful (15 ml) in six fluid ounces or more of water provides 40 mEq of potassium chloride.

One tablespoonful twice a day in six or more fluid ounces of water or other liquid provides 80 mEq potassium chloride.
Caution: Federal law prohibits dispensing without prescription.

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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg. (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

Boehringer Ingelheim
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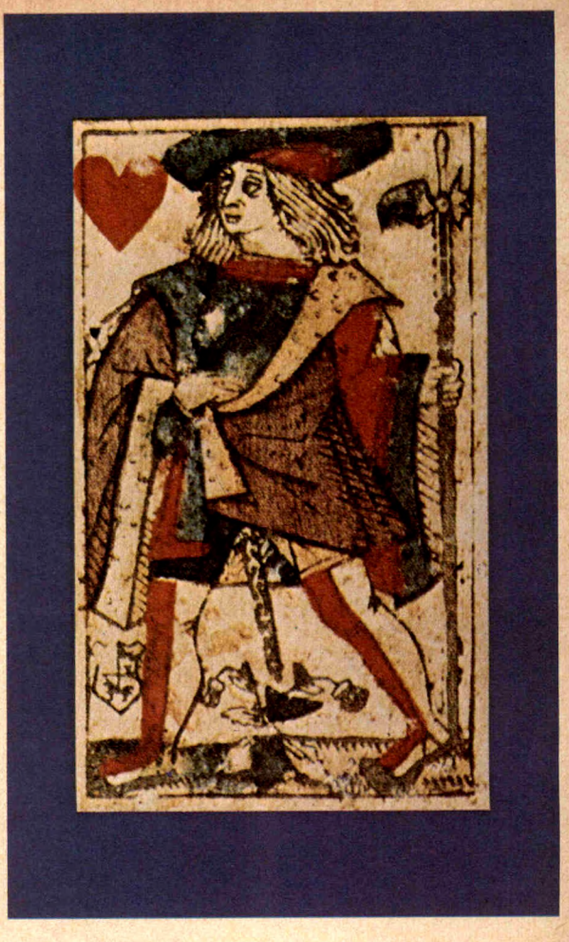

Illustrated: **Knave of Hearts**...from a series created in Rouen, France in the middle of the 16th century.

Only nine cards of this series survive, found intact in the binding of a 1544 edition of Dante. They were crafted in wood block and stencil colored.

Deutsches Spielkartenmuseum, Leinfelden

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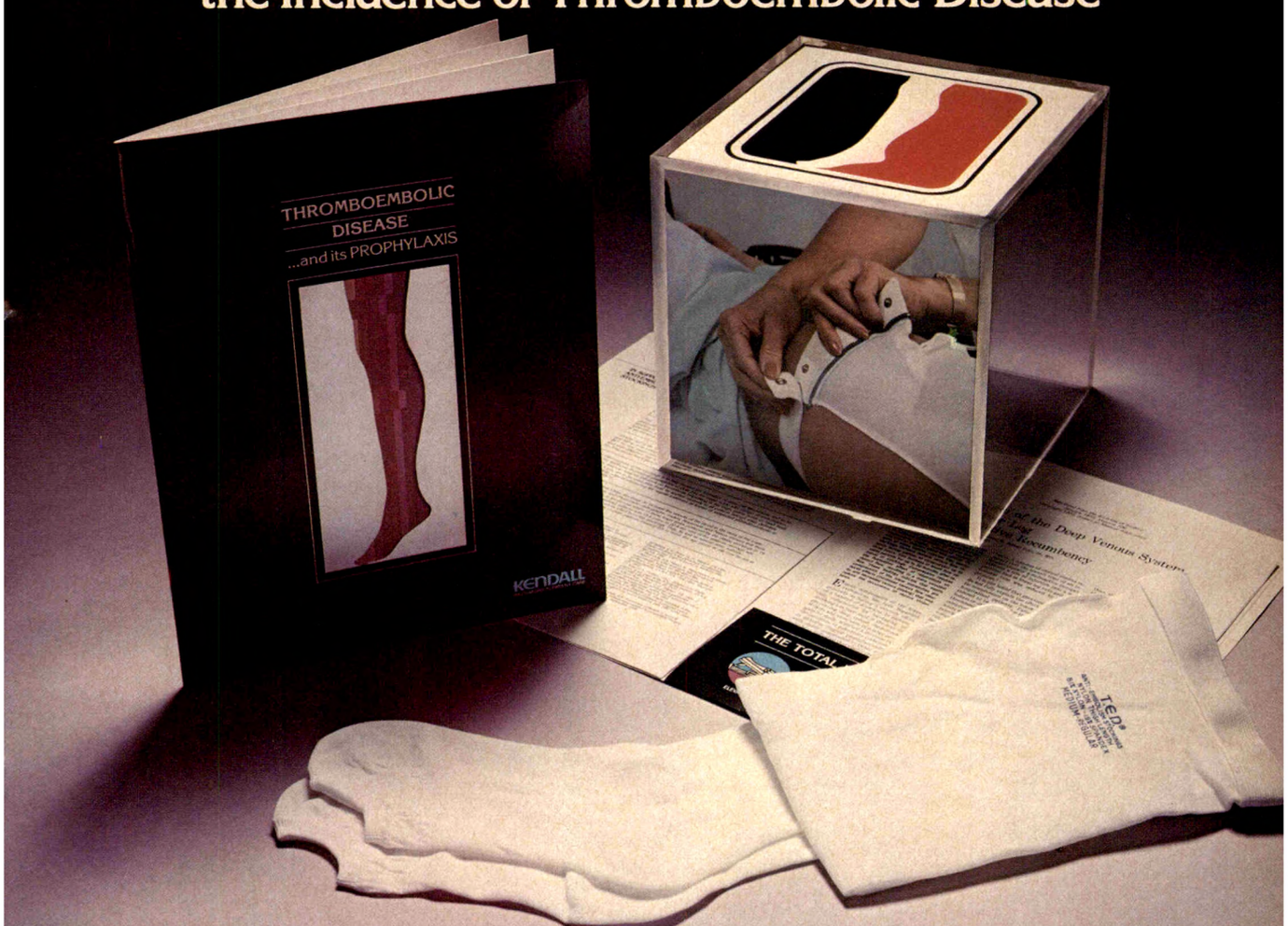

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Echocardiographic Spectrum of the Hypoplastic Left Heart Syndrome

A Clinicopathologic Correlation in 19 Newborns

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JAMES G. HENRY, MD
EDWARD W. GREEN, MD

Detroit, Michigan

Ultrasonic studies were performed in 19 neonates with the hypoplastic left heart syndrome whose diagnosis was confirmed at angiography or autopsy, or both. The patients were classified in two echocardiographic groups: Group I, 10 infants whose ventricular septum could be recorded, and Group II, 9 infants whose septum could not be recorded. The findings in these groups were compared with those in 60 neonates without congenital heart disease also studied with ultrasound. Two additional neonates who presented with signs of shock were also studied.

The diagnostic echocardiographic features of hypoplastic left heart syndrome were: (1) a left ventricular end-diastolic dimension of less than 9 mm; (2) an aortic root diameter of less than 6 mm; (3) a ratio of left ventricular end-diastolic to right ventricular end-diastolic dimension of less than 0.6; and (4) a mitral valve echo that is absent or greatly distorted and of small amplitude. These echocardiographic criteria differed significantly from findings in the normal group ($P < 0.01$). Echocardiography proved valuable in neonates with shock. It is a safe, reliable technique that can be used to delineate the intracardiac anatomy in sick neonates with the hypoplastic left heart syndrome.

"Hypoplastic left heart syndrome" is a term used to describe a wide spectrum of congenital heart defects consisting of small left ventricle, hypoplastic or atretic mitral valve, hypoplastic or atretic aortic valve, hypoplastic or interrupted aortic arch, with or without ventricular septal defect and with or without malposition of the great arteries.[1–4]

In this study we have defined the hypoplastic left heart syndrome as consisting of (1) aortic atresia, (2) mitral atresia or hypoplasia, (3) diminutive left ventricular cavity, (4) intact ventricular septum and (5) normally related great vessels. This paper presents the echocardiographic findings in 19 neonates with this syndrome and illustrates the value of echocardiography in the differential diagnosis of cardiogenic shock and congestive heart failure in this age group. For comparative analysis, 60 neonates without heart disease were also studied with ultrasound.

Material and Methods

The echocardiographic examinations were performed with a 5.0 megahertz transducer interfaced with a Smith-Kline Ekoline model 20 echocardiograph. All recordings were made on Polaroid® film. The technique of echocardiography in neonates is well established.[5–7] Nineteen newborn infants with the hypoplastic left heart syndrome were studied with standard ultrasonic technique. The diagnosis was confirmed by cardiac catheterization and biplane cineangiographic studies in 10 patients. The anteroposterior diameters of the ascending aorta and the aortic root at the level of the sinuses of Valsalva were measured with angiography in 10 patients. The intracardiac catheter was used as a reference point, and the measured values of the aortic diameters were corrected with use of a magnification factor. Autopsy was performed in 16 of 19 patients, and the ex-

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TABLE I

Nineteen Cases of Hypoplastic Left Heart Syndrome

Case no.	Age (days) at Echo	Age (days) at Death	Sex	Echocardiogram: ATL Ex (mm)	ATL E-F (mm/sec)	AML Ex (mm)	VS Motion	RVEDD (mm)	LVEDD (mm)	LAD (mm)	PAD (mm)	Ao (mm)	Cardiac Cath & Angio	Autopsy: AA	MA	MH	DLV
A. Group I																	
1	1	2	M	12	90	4	A	14	9	12	12	4.5	Yes	Yes	...	Yes	Yes
2	1	2	F	11	75	3	A	18	3	4	NR	4	No	Yes	...	Yes	Yes
3	1	1	F	15	80	NR	A	22	6	14	17	3	Yes	Yes	Yes	...	Yes
4	2	3	M	9	140	NR	B	14	3	9	11	4	No	Yes	Yes	...	Yes
5	2	2	M	10	50	NR	A	24	4	10	20	3	No	Yes	Yes	...	Yes
6	2	4	M	10	50	NR	A	15	5	11	NR	5	No	Yes	Yes	...	Yes
7	2	3	M	10	100	NR	B	12	6	9	NR	4	No	Yes	Yes	...	Yes
8	2	3	M	10	90	3	A	13	6	11	11	4	No	Yes	...	Yes	Yes
9	4	4	M	10	60	NR	B	20	4	12	12	4.5	Yes	Yes	Yes	...	Yes
10	4	6	F	13	80	NR	A	20	3	12	13	3	Yes	...	...	...	...
B. Group II																	
11	1	4	F	10	60	NR	...	...	...	9	NR	6	AA/MA	...	...	...	...
12	1	1	F	10	70	NR	...	...	...	NR	NR	NR	No	Yes	Yes	...	Absent
13	1	3	M	10	80	NR	...	...	...	NR	NR	NR	No	Yes	...	Yes	Yes
14	2	2	F	12	70	NR	...	...	...	10	NR	3.5	Yes	Yes	Yes	...	Absent
15	2	2	F	13	100	NR	...	...	...	10	NR	4.5	Yes	Yes	Yes	...	Absent
16	3	4	M	10	60	NR	...	...	...	10	10	4	Yes	Yes	Yes	...	Absent
17	3	6	M	10	80	NR	...	...	...	NR	NR	NR	No	Yes	Yes	...	Absent
18	4	5	M	11	75	NR	...	...	...	NR	NR	NR	Yes	Yes	...	Yes	Yes
19	9	21	M	11	80	NR	...	...	...	NR	NR	NR	AA/MA	...	...	...	...

A = reversed septal motion; AA = aortic atresia; AML = anterior mitral leaflet; Angio = angiography; Ao = aorta; ATL = anterior tricuspid leaflet; B = flat septal motion; Cath = cardiac catheterization; DLV = diminutive left ventricular cavity; Echo = echocardiography; E-F = closing slope; Ex = excursion; LAD = left atrial dimension; LVEDD = left ventricular end-diastolic dimension; MA = mitral atresia; MH = mitral hypoplasia; NR = not recorded; PAD = pulmonary arterial diameter; RVEDD = right ventricular end-diastolic dimension; VS = ventricular septum.

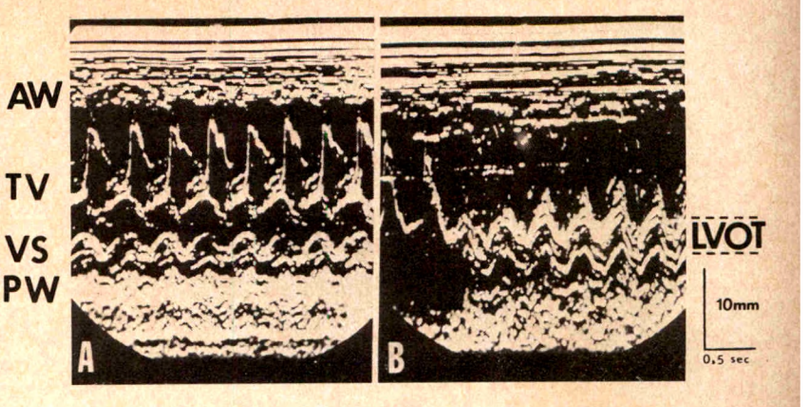

FIGURE 1. Case 2. Echocardiogram. **A**, a large right ventricle and a small left ventricle is seen. No mitral valve echo is seen. **B**, the transducer is rotated toward the aortic root, which is small. This patient had aortic atresia, mitral hypoplasia and a diminutive left ventricular cavity at autopsy. AW = anterior heart wall; LVOT = left ventricular outflow tract; PW = posterior wall of the left ventricle; TV = tricuspid valve; VS = ventricular septum. On original tracings ventrical and horizontal bars represented 10 mm deflection and 0.5 sec interval, respectively.

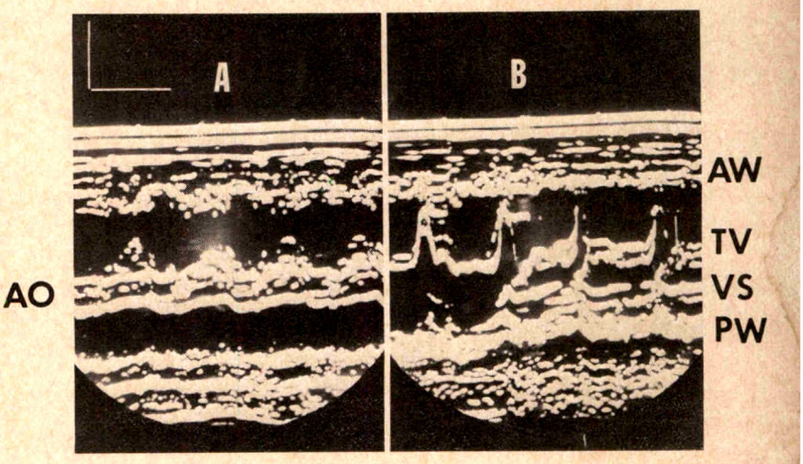

FIGURE 2. Case 4. Echocardiogram. **A**, a small aortic root is seen. **B**, a minute left ventricular cavity is demonstrated. No mitral valve is seen. This patient was proved to have aortic atresia, mitral atresia and a diminutive left ventricular cavity at autopsy. AO = aortic root; other abbreviations as in Figure 1.

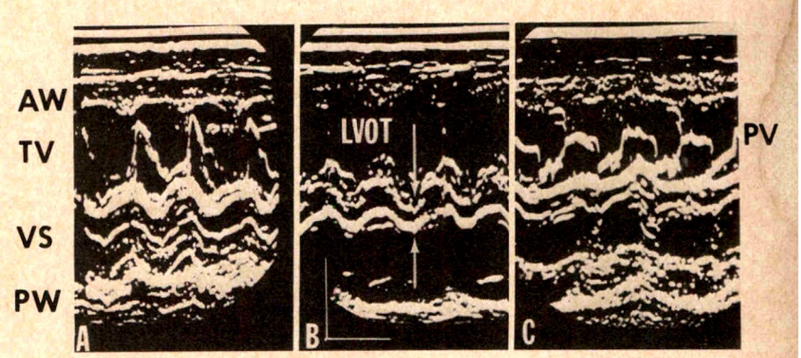

FIGURE 3. Case 8. Echocardiogram. **A**, the ventricular septal motion is reversed. The left ventricular end-diastolic dimension is small. The additional echo in the left ventricular cavity is assumed to arise from a rudimentary mitral valve. **B**, a small aortic root is seen (**arrows**). **C**, the pulmonary valve (PV) is recorded. This patient had mitral valve hypoplasia, aortic atresia and a diminutive left ventricle at autopsy. Abbreviations as in Figure 1.

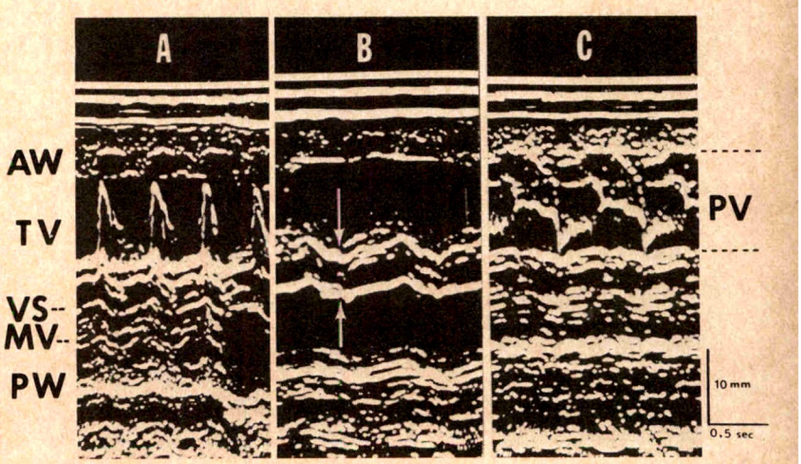

FIGURE 4. Case 1. Echocardiogram. **A**, an abnormal mitral valve (MV) echo is seen in the small left ventricular cavity. **B**, a small aortic root (**arrows**) is seen. **C**, the pulmonary valve is demonstrated. This patient had mitral valve hypoplasia, aortic atresia and a diminutive left ventricle at autopsy. Abbreviations as in Figure 1.

ternal diameter of the aorta, measured immediately above the sinuses of Valsalva, was available in 4 cases. A control group of 60 newborns without congenital heart disease was also studied with the standard echocardiographic technique. These patients ranged in age from 1 to 28 days (mean 4). Echocardiography was also performed in two additional infants who presented with signs of shock.

Clinical Features

The mean age of the 19 neonates was 2 days at the time of echocardiographic examination and 4 days at death. There were 12 male and 7 female infants. Seventeen patients presented with the clinical findings of cardiogenic shock. Two patients had a recordable blood pressure of 70/30 mm Hg in the legs at the time of the echocardiographic studies. In two patients a soft short midsystolic ejection murmur was heard along the left upper sternal border. All patients had a loud single second heart sound. Seventeen patients had right atrial and right ventricular enlargement, absent Q wave over the left precordium and right axis deviation in the routine electrocardiogram. Two patients had wide QRS complexes with intermediate axis deviation, and this finding was thought to reflect aberrant intraventricular conduction of nonspecific type, probably secondary to acidosis and hypoxia. No patient had left axis deviation. The chest roentgenogram in all patients revealed mild to moderate cardiac enlargement and various degrees of pulmonary venous congestion; three neonates had the reversed 5 sign due to loss of the shadow of the ascending aorta.

TABLE II

Measured Size of Aorta (mm)

Case no.	Echocardiogram (aortic root)	Angiogram		Autopsy (external diameter of asc aorta)
		Aortic Root	Asc Aorta	
1	4.5	4.0	3.5	NA
2	4.0	NA	NA	4.0
3	3.0	4.0	3.3	5.0
4	4.0	NA	NA	3.0
9	4.0	3.3	2.2	NA
10	3.0	2.9	2.2	NA
11	6.0	4.4	2.5	NA
14	3.5	3.5	2.8	NA
15	4.5	NA	NA	1.5
16	4.0	4.2	2.2	NA

Asc = ascending; NA = not available.

Results

The patients with hypoplastic left heart syndrome were classified in two echocardiographic groups (Table I): Group I, 10 patients whose ventricular septum was identifiable (Fig. 1 to 4); and Group II, 9 patients whose ventricular septum could not be identified by careful examination (Fig. 5 and 6).

The anterior tricuspid valve leaflet was recorded in all patients. The excursion of this leaflet ranged between 9 and 15 mm, and the E-F (closing) slope ranged between 50 and 140 mm/sec. The anterior mitral valve leaflet was identifiable in three patients only; its motion was abnormal, and its excursion was of low amplitude (Fig 4). The ventricular septal motion was type A (reversed) in 7 of the 10 patients in Group I and type B (flat) in the remaining 3. The echocardiographic dimensions of the aortic root were compared with the measured values either at autopsy or in the angiograms or both (Table II).

Figures 1 to 6 present the typical echocardiographic patterns of hypoplastic left heart syndrome. The structure labeled VS in Figures 1 to 4 is assumed to represent the ventricular septum. At autopsy, these four patients were proved to have a diminutive left ventricular cavity. The echo labeled MV in Figure 4 is assumed to represent an extremely hypoplastic mitral valve apparatus, on the basis of autopsy findings.

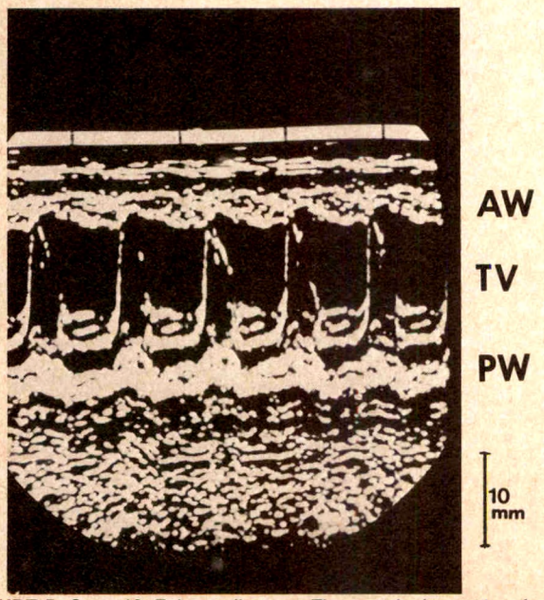

FIGURE 5. Case 16. Echocardiogram. The ventricular septum is not seen. A single large atrioventricular valvular motion is recorded, labeled tricuspid valve (TV). At autopsy, this patient was found to have mitral atresia, aortic atresia and no identifiable left ventricular cavity. Abbreviations as in Figure 1.

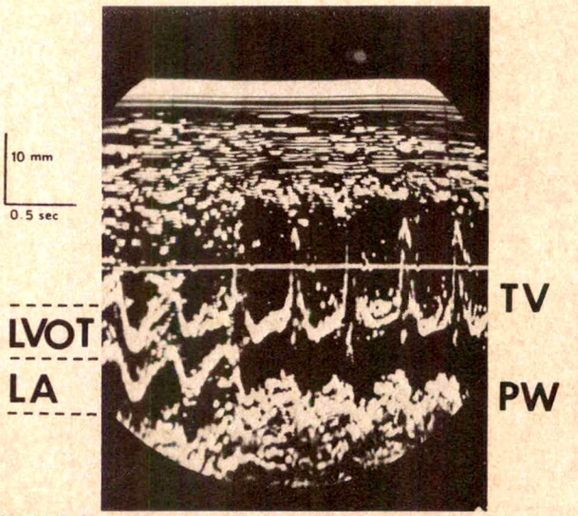

FIGURE 6. Case 15. Echocardiogram. The aorta is small and an echo of the type found in single ventricle was recorded. At autopsy, this patient was found to have aortic atresia, mitral atresia and absent left ventricular cavity. LA = left atrium; other abbreviations as in Figure 1.

Figures 7 and 8 show the echocardiograms of the two newborns who presented with signs of shock. Figure 7 is the ultrasonic study obtained in a 13 hour old newborn with severe congestive heart failure and absent pulses. The large left ventricular cavity (left ventricular to right ventricular end-diastolic dimension ratio 2.0) rules out the diagnosis of hypoplastic left heart syndrome. The mitral valve shows diminished excursion. This patient was found to have critical aortic valve stenosis at cardiac catheterization, and emergency aortic valvotomy was performed.

Figure 8 is the ultrasonic study obtained in a 10 hour old neonate with shock. The possibility of hypoplastic left heart syndrome was ruled out by this study. The

TABLE III

Comparison of Echocardiographic Findings in 19 Neonates With Hypoplastic Left Heart Syndrome and 60 Neonates Without Congenital Heart Defect

	Normal Neonates		Hypoplastic Left Heart Syndrome		
Echocardiographic Variables	Range	Mean ± SD	Range	Mean ± SD	*P* Value
LVEDD (mm)	10.00–27.00	14.82 ± 3.04	3.00–9.00	4.90 ± 1.91	<0.01*
RVEDD (mm)	4.00–16.00	8.53 ± 2.37	12.00–24.00	17.20 ± 4.16	<0.01*
LVEDD/RVEDD ratio	1.00–4.5	1.89 ± 0.75	0.15–0.64	0.31 ± 0.17	<0.01*
Aorta (mm)	7.00–12.00	9.18 ± 1.03	3.00–6.00	4.07 ± 0.83	<0.01*
LAD (mm)	7.00–15.00	9.98 ± 1.57	4.00–14.00	10.21 ± 2.29	>0.05†

* Highly significant.
† Insignificant.
LAD = left atrial dimension; LVEDD = left ventricular end-diastolic dimension; *P* = probability; RVEDD = right ventricular end-diastolic dimension; SD = standard deviation.

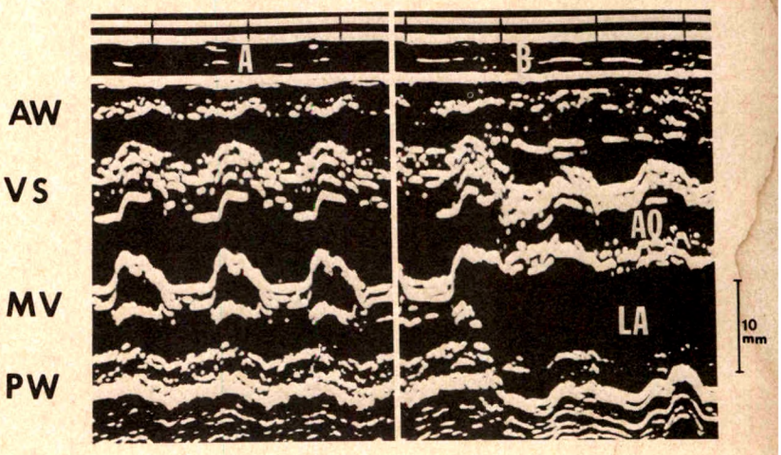

FIGURE 7. Echocardiogram from a neonate with critical aortic valve stenosis, congestive heart failure and no recordable pulses. The left ventricle is larger than normal and the aortic root (AO) is of normal size. Both leaflets of the mitral valve (MV) are recorded. LA = left atrium; other abbreviations as in Figure 1.

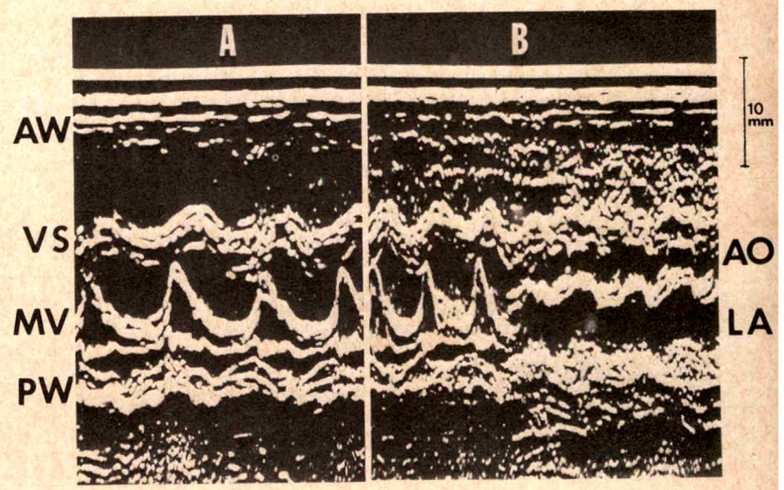

FIGURE 8. Echocardiogram from a neonate with clinical findings of shock secondary to cerebral hemorrhage. The mitral valve (MV), left ventricular cavity, aortic root (AO) and the left atrium (LA) are of normal size. Abbreviations as in Figure 1.

TABLE IV

Echocardiographic Data in Normal Neonates and Infants

Study	Aortic Root (mm)	LVEDD (mm)	RVEDD (mm)	LAD (mm)
Meyer and Kaplan[7]	7–12	12–20 (16)	10–17 (13)	6–13 (9)
Solinger et al.[5]	9–11	15.8–21.4	10.1–14.3	6.5–10.2
Hagan et al.[6]	8.1–12.0 (10.0)	12–23.3 (18.7)	6.1–15.0 (11.4)	5.0–10.0 (7.0)
Godman et al.[8]	8.0–11.0 (10.2)	12.0–20.4 (16.2)	10.0–17.5 (13.8)	4.0–10.5 (6.4)
Lortscher et al.[10]	8–13 (10)	9–19 (15)	7–20 (14)	3–8 (5.5)
Lundstrom[9]	8–19	12–31	4–11	7–22
Present series	7.0–12.0 (9.18 ± 1.03)	10.0–27.0 (14.8 ± 3.04)	4.0–16.0 (8.53 ± 2.37)	7.0–15.0 (9.98 ± 1.57)

Figures in parentheses indicate mean values (± standard deviation in present series).
LAD = left atrial dimension; LVEDD = left ventricular end-diastolic dimension; RVEDD = right ventricular end-diastolic dimension.

baby died at age 20 hours and was found to have normal cardiac anatomy. The cause of death was intracerebral hemorrhage.

Table III compares the echocardiographic findings in the 60 neonates without congenital heart defect and our 19 patients with the hypoplastic left heart syndrome. The left and right ventricular dimensions and ratios and aortic dimensions were significantly different ($P < 0.01$). However, the left atrial dimension did not differ significantly ($P > 0.05$). The values in our normal neonates were comparable with those reported by others[5–10] (Table IV).

TABLE V

Echocardiographic Data in Hypoplastic Left Heart Syndrome

Echocardiographic Findings	Meyer et al.[7] (6 patients)	Godman et al.[8] (12 patients)	Present Series (19 patients)
Dimensions (mm)			
Left ventricular end-diastolic	4–9	3–11 [8 pts]	3–9 (4.9 ± 1.91)
Right ventricular end-diastolic	22–32 (25)	20–32	12–24 (17.20 ± 4.16)
Aortic	NR	4–7 [5 pts]	3–6 (4.07 ± 0.83)
Left atrial	NR	NR	4–14 (10.21 ± 2.29)
Tricuspid valve excursion (mm)	10–13 [5 pts]	10–15	9–15 (10.89 ± 1.49)
E-F slope (mm/sec)	29–78 [4 pts]	NR	50–140 (78.42 ± 20.82)
Mitral valve excursion (mm)	3–5 [4 pts]	3–8 [6 pts]	NR
E-F slope (mm/sec)	28 [1 pt]	NR	NR
"Single ventricle" type	None	4 pts	9 pts

Figures in parentheses indicate mean values (± standard deviation in present series).
NR = not reported or recorded; pts = patients.

Discussion

The hypoplastic left heart syndrome accounts for only 1.2 percent of all congenital heart defects,[11] but it is the most common congenital heart defect resulting in congestive heart failure and death within the 1st month of life.[12,13] Its incidence rate may be as high as 15 percent of all autopsy cases of congenital heart defect.[4] A male/female ratio of 2:1 has been reported.[14] Patients with the syndrome present with severe congestive heart failure within the 1st few days of life. The pulses are absent or feeble, but the right ventricular thrust is prominent on precordial examination. The degree of cyanosis is quite variable, and the skin color is usually ash grey. Characteristically there are no murmurs, and the second heart sound is loud and single. The chest roentgenogram is usually nonspecific but a reversed 5 sign, when present, may be helpful.[15] The electrocardiographic features suggest right ventricular hypertrophy and right atrial enlargement, and may mimick left ventricular hypertrophy in rare cases.[16] Cardiac catheterization and angiography have been used to make a definitive diagnosis.[17]

The echocardiographic findings in the hypoplastic left heart syndrome are quite uniform[7,8,18,19] and include: (1) a small left ventricular cavity, (2) a small aortic root, (3) absent or distorted mitral valve echo, (4) absence of ventricular septal echo, and (5) a single atrioventricular valve. In our study we classified the patients in two echocardiographic groups.

Group I: In this group of 10 patients whose ventricular septum could be demonstrated (Table IA) the left ventricular cavity was significantly smaller than in normal neonates. The mitral valve was recorded in only three patients. Its excursion was small and the E-F slope could not be measured in any patient. On autopsy these three patients had mitral valve hypoplasia rather than atresia. Six other patients in this group who underwent autopsy had mitral and aortic atresia and a diminutive left ventricular cavity.

Group II: In this group, the remaining nine patients whose ventricular septum could not be recorded (Table IB), a large single atrioventricular valve was recorded in all. In five of seven who underwent autopsy examination, the left ventricular cavity was not identifiable.

In the remaining two patients a slit-like left ventricular cavity was seen on autopsy. However, the ventricular septum was not recorded in these two patients by ultrasonic examination.

Comparison of echocardiographic and angiographic aortic dimensions: The dimensions of the aorta as measured with echocardiography and angiography and at autopsy (Table II) were compared. Although there was an apparent gross correlation between the echocardiographic and angiographic measurements of the aorta, the former values tended to be greater than those measured with angiography or at autopsy. This apparent discrepancy may be due to several factors: (1) The aortic root is distended during life, (2) the aortic root usually resembles an hourglass in angiograms, and (3) it is difficult to ascertain the exact direction of the ultrasonic beam.

Table V compares our echocardiographic findings in the hypoplastic left heart syndrome with those of two other reported series.[7,8] Our data are comparable.

In conclusion, we believe that echocardiography is helpful in the newborn age group and can be reliably, safely and rapidly utilized to distinguish cardiogenic shock and congestive heart failure due to the hypoplastic left heart syndrome from other cardiac and noncardiac conditions associated with absent pulses (Fig. 7 and 8).

Acknowledgment

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Surgical Correction in Complete Levotransposition of the Great Arteries With an Unusual Subaortic Ventricular Septal Defect

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Six children with an uncommon variant of complete (that is, physiologically uncorrected) transposition of the great arteries are described. In this malformation, levoposition of the aorta is coincident with situs solitus and concordant atrioventricular relations. All patients underwent successful surgical correction. Four had a ventricular septal defect; in three, the defect was subaortic and because of its unusual anatomic features, a right ventriculotomy was required for repair. Interatrial transposition of venous return was carried out in all cases by insertion of a baffle, as in complete dextrotransposition of the great arteries. The surgical verification of the arterial positions in these cases illustrated the fallibility of the so-called loop rule. The significance of the cases in relation to terminology, classification and morphogenesis of this variant is discussed.

There is dispute concerning the incidence of a levopositioned transposed aorta in association with situs solitus and atrioventricular concordance. Paul et al.[1] considered this variant rare, stating that it was unusual to find other than a dextrotransposed aorta with a *d*-bulboventricular loop (the "loop rule"). Although Carr et al.[2] reported that this rule was contravened in at least 17 percent of their cases, acceptance of the existence of *l*-transposition with concordant atrioventricular relation (complete *l*-transposition) is not widespread.[3] Descriptions of surgical correction of this type of transposition are few, particularly when this lesion is associated with a ventricular septal defect. We have now successfully operated on six children with this form of transposition, four of whom had an associated ventricular septal defect (Table I). The anatomic features of the defect in three cases were unusual and significantly influenced the surgical approach.

In view of the satisfactory surgical treatment of these patients continuing interest in the terminology and morphogenesis of transposition of the great vessels,[4] we document herein the clinical, angiocardiographic and surgical features of this variant of "complete" transposition.

Reports of Cases

Case 1

This male infant had cyanosis from birth and was transferred to the Brompton Hospital on the 1st day of life with a diagnosis of complex congenital heart disease.

Clinical findings: He was cyanotic and tachypneic. The jugular venous pressure was normal. The first and second heart sounds were normal, and a grade 2/4 systolic ejection murmur was heard at the left sternal edge. The hemoglobin was 16.9 g/100 ml.

The electrocardiogram revealed sinus rhythm with a QRS axis of +150° and right ventricular hypertrophy. The chest roentgenogram showed mild enlargement of the heart and plethoric lung fields. The pulmonary vessels appeared to taper evenly into the periphery.

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TABLE I

Six Cases With Uncorrected Transposition and /-Position of the Aorta

Case no.	Sex	Date of Birth (mo/day/yr)	BAS	Associated Cardiac Lesions	Age at Operation (months)	ASD Present at Operation	Surgical Procedure	Bypass Technique
1	M	12/5/71	12/5/71	VSD (subaortic)	29	Small PFO	Interatrial baffle, transventricular repair of VSD	CPB + CA
2	M	10/22/72	No	VSD (subaortic)	21	No	Interatrial baffle, transventricular repair of VSD	CPB + CA
3	F	7/20/72	No	VSD (subaortic) + PDA*	28	No	Interatrial baffle, transventricular repair of VSD	CA
4	M	1/22/70	No	Malalignment VSD	55	No	Interatrial baffle, transvalvular repair of VSD	CPB + CA
5	M	8/29/73	8/30/73	ASD	10	Moderate size	Interatrial baffle	CA
6	M	4/5/72	4/21/72	ASD	18	Moderate size	Interatrial baffle	CPB

ASD = atrial septal defect; BAS = balloon atrial septostomy; CA = circulatory arrest and profound hypothermia; CPB = cardiopulmonary bypass; PDA = patent ductus arteriosus; PFO = patent foramen ovale; VSD = ventricular septal defect.
*Patent ductus arteriosus was ligated elsewhere and the pulmonary artery was banded at the same time.

TABLE II

Cardiac Catheterization Data in Six Cases

Case no.	Oxygen Saturation (%)*								Pressures (mm Hg)					
	SVC	IVC	RA	LA	RV	LV	Ao	MPA	RA†	LA†	RV	LV	Ao	MPA
1a	40	—	38	98	29	—	43	—	3	—	69	—	66/51	—
b	24	23	21	—	25	—	32	—	8	—	70/	—	67/42	
2	50	55	57	—	58	—	65	—	4	—	85/4	—	85/50	—
3a	57	71	77.5	96.8	77.5	—	84	—	6	8	55/5	—	70/45	—
b	49	32	50	—	—	55	—	—	10	9	—	70/0	—	33/22
4	51	46	50	—	60	98	66	91	13	—	85/	83/	85/60	43/21
5	48	51	54	90	65	92	65	71	2	3	60/3	44/0	60/45	43/19
6a	—	26	29	94	25	72	31	84	5	11	63/0	50/0	65/35	50/25
b	38	39	75	96	60	96	73	86	3	4	80/0	40/0	85/55	28/16

Ao = aorta; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; MPA = main pulmonary artery; RA = right atrium; RV = right ventricle; SVC = superior vena cava.
*Inspired oxygen concentration 25 percent.
†Mean pressure.

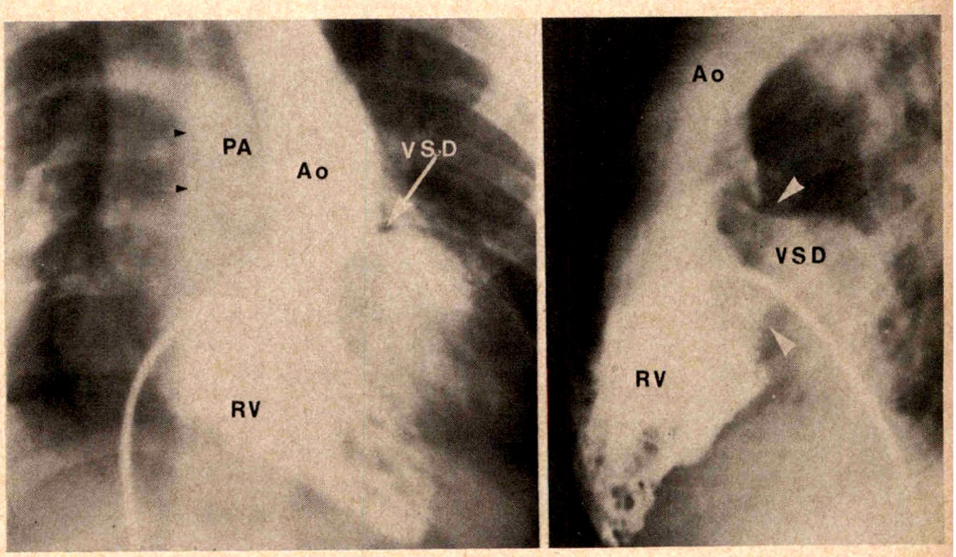

FIGURE 1. Case 1. Anteroposterior and lateral right ventricular angiocardiogram. The aorta (Ao) arises from the morphologic right ventricle (RV). The ventricular septal defect (VSD) is immediately subaortic as seen in the backflow from the right ventricle. The pulmonary artery (PA) is faintly opacified and is to the right of the aorta.

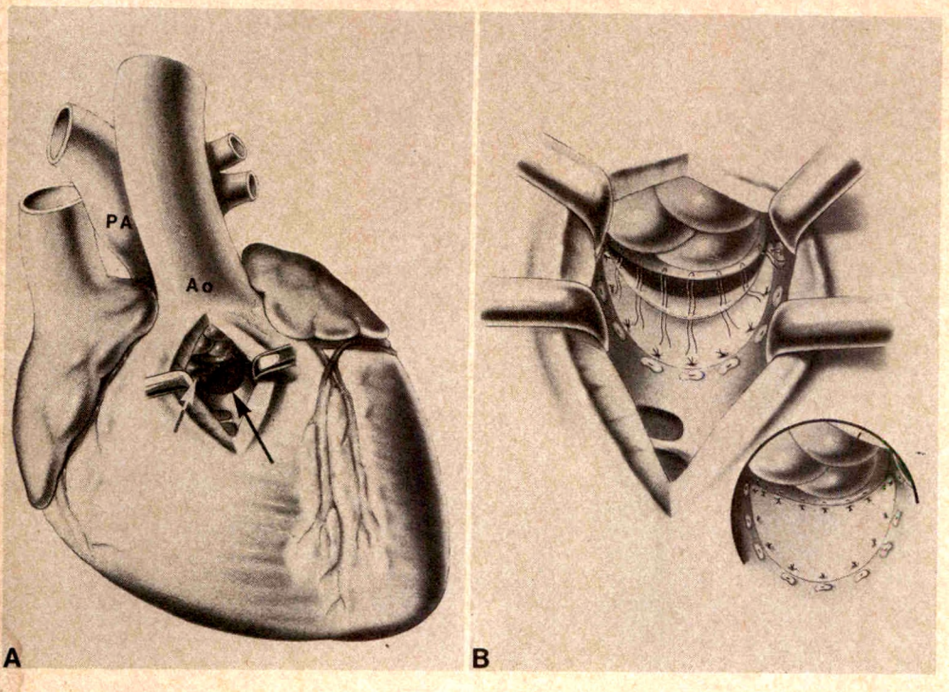

FIGURE 2. Case 1. Artist's drawing of the heart at operation. **A,** external aspect of the heart and the great vessels showing the left-sided aorta (Ao) and the vertical incision in the right ventricular outflow tract. The immediate subaortic position of the ventricular septal defect is shown **(black arrow).** The pulmonary valve can be seen below posteriorly and to the right of the aortic valve **(white arrow). B,** the inferior margin of the patch to close the ventricular septal defect is attached to the crest of the muscular septum and the superior margin to the posterior half of the aortic valve ring.

Special investigation: Cardiac catheterization data are shown in Table II. Angiocardiography disclosed atrioventricular concordance with situs solitus. The aorta, which arose from the morphologic right ventricle, was positioned to the left of the main pulmonary artery, which arose from the morphologic left ventricle. There was a subaortic ventricular septal defect (Fig. 1). Results of a balloon atrial septostomy, performed at this time were good.

The child thrived, and was readmitted at age 29 months for corrective surgery. Examination revealed that the second heart sound was now split, with an accentuated pulmonary component. Repeat cardiac catheterization and angiocardiography were carried out but, as previously, the main pulmonary artery could not be entered.

Treatment: At operation, the angiocardiographic appearance of the great vessels was confirmed. The aorta and the aortic valve were to the left of the main pulmonary artery and pulmonary valve ring.

Routine cardiopulmonary bypass and hypothermia with intermittent cardiac ischemia were used during the corrective procedure. Because the ventricular septal defect was not visualized after inspection through the tricuspid valve, an incision was made high in the infundibulum of the right ventricle. It was then seen that the defect was in the coronal plane and that it was immediately subaortic. Its inferior edge was formed by the crest of the ventricular septum and the superior edge by the posterior half of the inferior free margin of the aortic root. The papillary muscle of the conus was well seen posteroinferior to the defect (Fig. 2A). The defect was closed with use of a Dacron® patch; the upper part was attached to the under surface of the posterior half of the aortic valve ring, and the lower part to the muscular interventricular septum (Fig. 2B).

Venous inflow at the atrial level was rerouted, using an interatrial baffle of thin Teflon® (USCI 3106) after the design of Brom et al.[5] Briefly, the baffle is cut in a "trouser" shape. The "waist" is attached to the posterior wall of the left atrium to incorporate the pulmonary veins. The "legs" of the patch, which have a width three fourths the circumference of the superior and and inferior venae cavae, form the roof of the inflow tract for the blood from the great veins. This shape gives a smooth configuration whether the baffle is made of pericardium or synthetic cloth.

The pulmonary venous atrium was generously enlarged by the insertion of an inlay patch in the right lateral wall of this chamber.

The child was discharged from the hospital 2 weeks after operation. At follow-up 18 months later, he was asymptomatic. The heart was still slightly enlarged and an early diastolic murmur was heard maximal at the second left intercostal space. These findings probably represent mild aortic incompetence secondary to the repair.

Case 2

This boy was admitted at age 21 months with a clinical diagnosis of cyanotic congenital heart disease.

Clinical findings: There was marked clubbing of the fingers and toes, and examination revealed a hyperactive right ventricle. The first and second heart sounds were single, and grade 2/4 systolic ejection murmur was well heard at the left sternal edge. The hemoglobin was 18.0 g/100 ml.

The electrocardiogram revealed sinus rhythm with a QRS axis of +120°. Biatrial and right ventricular hypertrophy was present. Chest roentgenograms revealed an enlarged heart, and displacement of the trachea to the right. The lung fields were plethoric. The upper mediastinum was widened, probably because of an enlarged thymus.

Special investigation: Cardiac catheterization data are shown in Table II. Angiocardiography disclosed situs solitus with atrioventricular concordance and transposition of the great arteries with the aorta in *l*-position. There was a subaortic ventricular septal defect.

Treatment: At operation, the ventricular septal defect could be seen only through a right ventriculotomy; its anatomy was identical to that described in Case 1. Closure was also as described in that case. The atrial septum was intact and, after

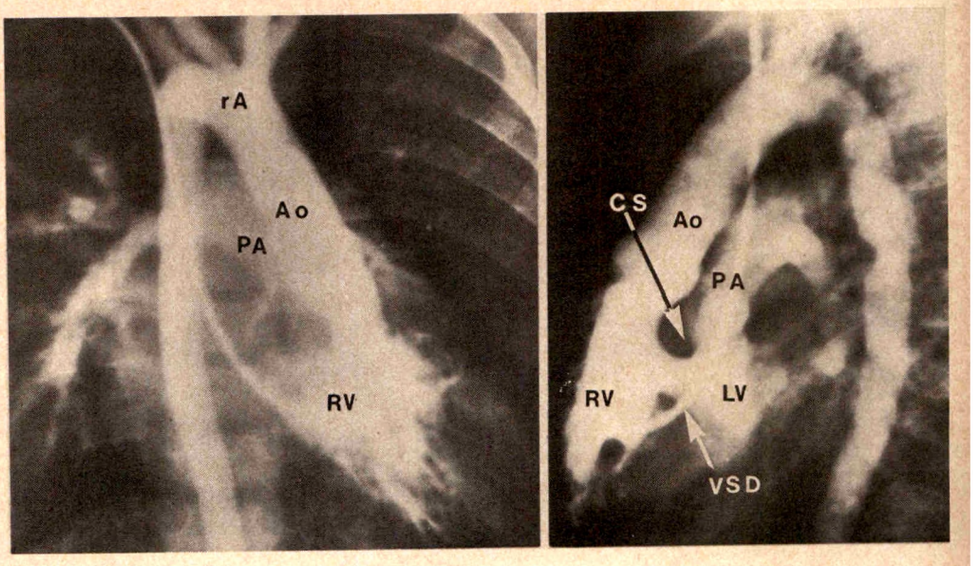

FIGURE 3. Case 4. Anteroposterior and lateral right ventricular angiocardiogram. The aorta (Ao) arises from the right ventricle (RV) and is to the left of the main pulmonary artery (PA), opacified by the backflow through the ventricular septal defect (VSD). Note the well-marked conal septum (CS). Note also, the right aortic arch (rA) with inversion of the head vessels. LV = left ventricle.

partial resection of this structure, interatrial rerouting of blood was carried out as in Case 1.

The child had an uneventful postoperative course, and was discharged 3 weeks after operation. He remains well and asymptomatic 1 year after discharge.

Case 3

This girl, cyanotic from birth, was first investigated in another hospital at age 1 week. Diagnosis of transposition of the great arteries with a high ventricular septal defect, an atrial septal defect and a patent ductus arteriosus was established. Because her condition deteriorated within a few weeks, closure of the patent ductus arteriosus and banding of the pulmonary artery were carried out. She was later admitted to the Brompton Hospital at age 28 months.

Clinical findings: She was a small child with severe cyanosis, clubbing of the fingers and toes and bulging of the sternum. She was ranked below the third percentile for weight and height. A grade 2/4 systolic ejection murmur was best heard at the lower left sternal border. The second heart sound was single. The hemoglobin was 20.6 g/100 ml.

The electrocardiogram exhibited sinus rhythm with a QRS axis of +170°, together with right atrial and right ventricular hypertrophy. The heart was enlarged as judged from the chest roentgenogram, and the lung fields were plethoric.

Special investigation: Repeat preoperative cardiac catheterization was carried out (Table II). Angiocardiography revealed situs solitus, atrioventricular concordance and *l*-transposition of the great arteries with a subaortic ventricular septal defect. The pulmonary artery, which arose from the morphologic left ventricle, was to the right and posterior to the aorta and was slightly opacified by contrast medium from the right ventricle passing through the defect.

Treatment: With use of profound hypothermia and circulatory arrest, the ventricular septal defect was closed through a transventricular approach in the manner described in Case 1, since again its upper border was formed by the aortic root. The pulmonary artery was of good size, and no evidence of the pulmonary arterial band was found. Interatrial rerouting of the venous inflow was performed after resection of the intact atrial septum.

One year after operation the patient is asymptomatic and well.

Case 4

This male infant, cyanotic at birth, was admitted to our hospital 2 weeks later.

Clinical findings: Cyanosis, hepatomegaly and peripheral edema were present. The jugular venous pressure was increased. A grade 2/4 systolic ejection murmur was audible at the left sternal edge. The remaining clinical findings were normal. Hemoglobin was 16.7 g/100 ml.

The electrocardiogram revealed sinus rhythm with a QRS axis of −130°. Right atrial and mild right ventricular hypertrophy was present. The chest roentgenogram revealed slight cardiomegaly with plethoric lung fields. Displacement of the trachea to the left suggested a right aortic arch. Despite plethora, the main pulmonary artery was not visible.

Special investigation: Cardiac catheterization data are presented in Table II. Angiocardiography revealed situs solitus, atrioventricular concordance and *l*-transposition of the great arteries. A large ventricular septal defect was identified inferior to a well marked conal septum. A small patent ductus arteriosus was present, and there was mild pulmonary stenosis (Fig. 3).

Treatment: Definitive surgical correction was delayed until the child was 4 years, 7 months old. The external appearance of the heart and great vessels were as shown in Figure 4. Profound hypothermia and circulatory arrest were used to carry out the intracardiac repair. The ventricular septal defect was easily seen through the tricuspid valve, and was situated between the conal septum and the anterior ventricular septum. It thus possessed completely muscular walls, and was closed through the tricuspid valve in the routine way. Interatrial rerouting of blood by means of an interatrial baffle was then carried out as in Case 1.

Four days after operation the child had a grand mal seizure, but thereafter made an uninterrupted postoperative recovery and was discharged from hospital 21 days after admission. When seen 15 months after operation he was asymptomatic and well.

Case 5

This male infant was transferred to the Brompton Hospital because of severe cyanosis that was present from birth.

Clinical findings: The infant was considered moribund with severe cyanosis and dyspnea. The heart sounds were normal and no murmurs were audible. The hemoglobin was 18.7 g/100 ml.

The electrocardiogram revealed sinus rhythm with a QRS axis of +150° and evidence of right ventricular hypertrophy. Chest roentgenograms disclosed an enlarged heart that was displaced to the left. Only the right lung vessels were seen, and these appeared to be slightly plethoric.

Special investigation: Cardiac catheterization data are seen in Table II. Angiocardiography revealed the presence of situs solitus, concordant atrioventricular relations and *l*-transposition of the great arteries. A patent foramen ovale and patent ductus arteriosus were both present, but the ventricular septum was intact. At this investigation a balloon atrial septostomy was performed, with good effect.

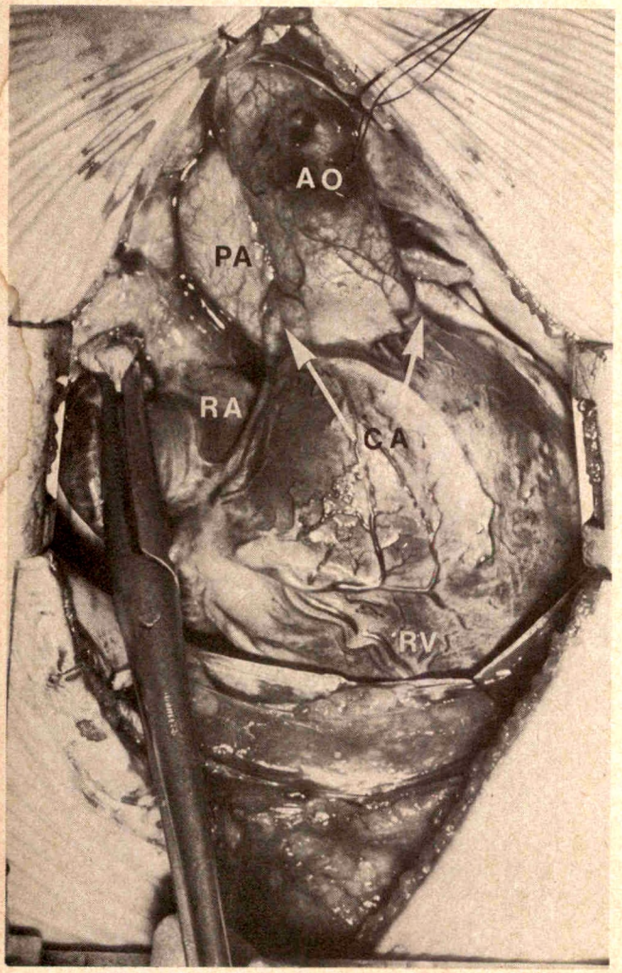

FIGURE 4. Case 4. Intraoperative aspect of the heart and the great vessels. The aorta (Ao) is anterior and to the left of the main pulmonary artery (PA). Note the coronary arteries (**white arrows,** CA). Compare with this patient's angiocardiograms in Figure 3.

Treatment: After repeated upper respiratory tract infections, the child underwent total correction of his cardiac anomaly at age 10 months. By then, the patent ductus arteriosus had closed. The external appearance of the heart confirmed that the aorta and the aortic valve were to the left of the main pulmonary artery. The atrial septal defect was enlarged, and rerouting of blood at the atrial level was carried out as previously described.

The child was discharged 18 days after operation; when seen 15 months later, he was asymptomatic and well.

Case 6

This male infant was transferred to the hospital at age 2 weeks because of poor feeding, dyspnea and cyanosis.

Clinical findings: The infant was cyanotic. The heart sounds were each single. A right ventricular impulse was palpable. A grade 2/4 systolic ejection murmur was audible at the left sternal edge. The liver was enlarged. Hemoglobin was 12.5 g/100 ml.

The electrocardiogram demonstrated sinus rhythm with a QRS axis of +130° and mild ventricular hypertrophy. The chest roentgenogram revealed marked enlargement of the heart and plethoric lung fields. The left heart border was straight, suggesting the presence of a left-sided aorta.

Special investigation: Cardiac catherization data are shown in Table II. Angiocardiography demonstrated situs solitus, atrioventricular concordance and *l*-transposition of the great arteries with a small ventricular septal defect. A balloon atrial septostomy resulted in good clinical improvement. In a repeat investigation, performed at age 18 months, the ventricular septal defect was found to be closed (Fig. 5, A and B).

Treatment: Surgical correction of the anomaly was carried out by enlargement of the patent foramen ovale and placement of an interatrial baffle for the rerouting of venous inflow of blood.

This child was discharged 14 days after operation. He has since been followed up for 2 years and is asymptomatic and well.

Discussion

All six patients manifested situs solitus in association with atrioventricular concordance and transposition of the aorta and pulmonary artery. Therefore, complete transposition of the great arteries was physiologically present. However, in each case the aorta and the aortic valve were to the left of the pulmonary artery and valve, occupying the position more usually associated with physiologically corrected transposition. Despite this unusual aortic position, the cases presented as would be expected for complete transposition. Thus, all patients had signs of severe cyanosis, and most became severely ill soon after birth. As judged by chest roentgenogram, cardiomegaly and pulmonary plethora were present in all cases. However, an unusual roentgenographic feature for complete transposition, a straight left heart border, was observed in half of our cases. The electrocardiographic characteristics were typical of complete transposition except for an unexplained superior QRS axis (−130°) in one case.

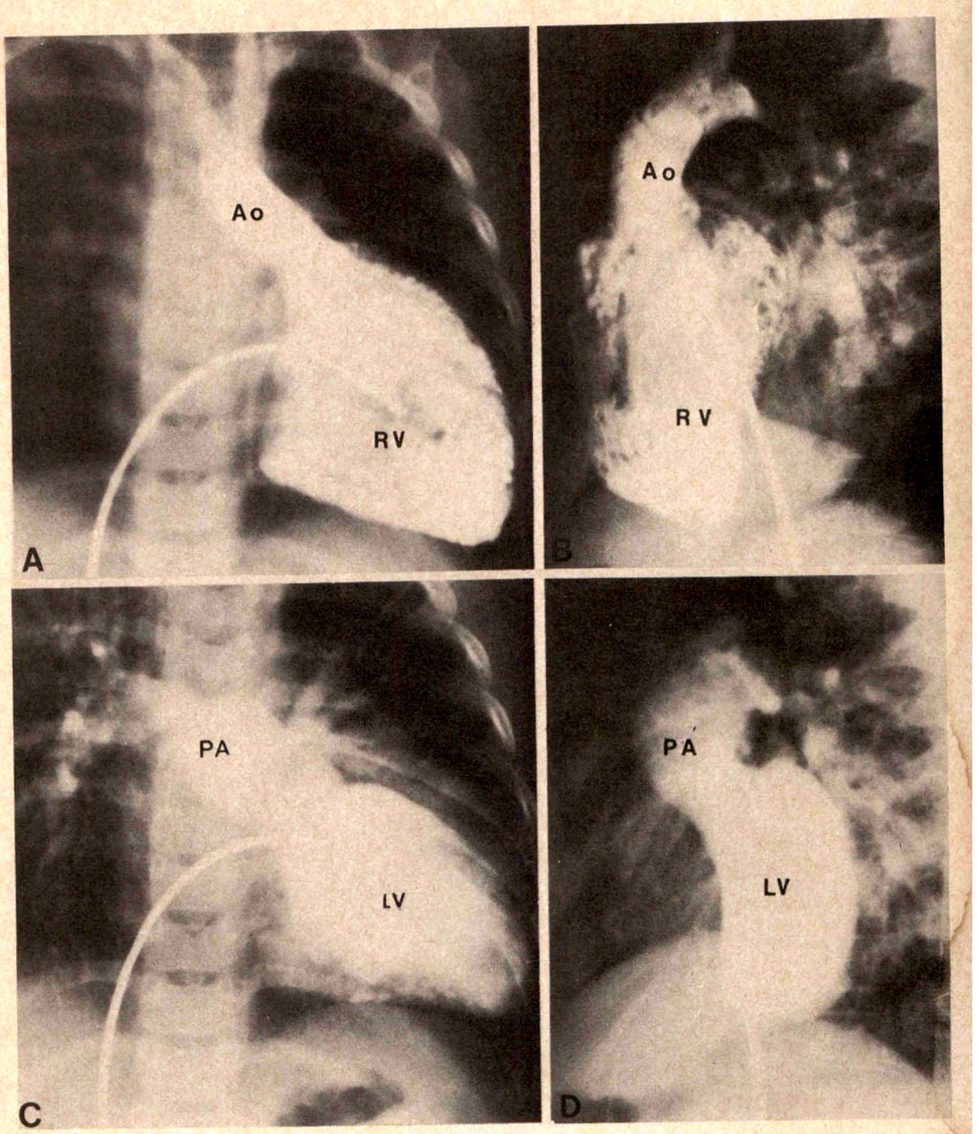

FIGURE 5. Case 6. Angiocardiograms. **A and B,** anteroposterior and lateral right ventricular angiocardiogram. The aorta (Ao) arises from a morphologic right ventricle (RV). **C and D,** the left ventricular angiocardiogram shows that the pulmonary artery (PA) arises from the morphologic left ventricle (LV) but lies to the right of the aorta.

In all six cases, both a left-sided aorta and atrioventricular concordance were conclusively demonstrated with angiocardiography (Fig. 1 and 3 to 6). Our data thus indicate that the left-sided aorta is of little clinical significance. Indeed, in our Cases 4 to 6, the unusual aortic position did not alter surgical management. In Case 4 a malalignment defect was closed by way of the tricuspid valve, and in Cases 5 and 6 routine intraatrial rerouting of venous return was performed. In these cases, therefore, the *l*-positioned aorta had primary significance for classification and terminology, as will be discussed later. However, in our first three cases, the finding of a subaortic defect made it necessary to use a ventricular approach to effect closure. Idriss et al.[6] in their recent study suggest that such defects are rare in complete transposition; they encountered only 8 in 86 cases, and did not specify whether the aorta in those cases was right- or left-sided. It is surprising that in our small series of six cases with complete *l*-transposition, half should have such a high subaortic defect, and it is noteworthy that Quero-Jiminez and Perez Martinez[7] have recently described this same combination. We will therefore consider its significance for surgical management in more detail before discussing the significance of the *l*-transposed aorta in relation to terminology and classification.

Surgical Management

Profound hypothermia and circulatory arrest[8] were used to allow the intracardiac repair in these cases but, in Cases 1 to 4, routine cardiopulmonary bypass was additionally used because the intracardiac repair could not be achieved within 60 minutes. In all cases, an intraatrial baffle was routinely placed as for complete transposition since these cases are indeed examples of complete transposition. When an associated ventricular

septal defect was present, closure was first attempted through the tricuspid valve since this procedure is usually successful in complete transposition.[6] However, in Cases 1 to 3, the defect could not be seen by this route and could be located only through a right ventriculotomy high in the infundibulum of the right ventricle, immediately inferior to the aortic valve ring (Fig. 2). The subsequent absence of right heart failure in the postoperative period in these patients was attributed to this high position of the ventriculotomy, which places the incision in the "least" contractile part of the important systemic ventricle.

In addition to their unusual position, the septal defects also presented unusual problems for closure. The boundaries were inferiorly the crest of the ventricular septum and superiorly the under side of the posterior half of the aortic valve (Fig. 2B). Closure could therefore be achieved only by attaching the patch to the under side of the aortic valve ring proper and also to the superior border of the crest of the septum (Fig. 2B). None of our patients had severe pulmonary stenosis. However, Imamura et al.[9] have described two patients who had *d*-transposition and a subaortic ventricular septal defect. Both patients had severe pulmonary stenosis, and total correction was achieved with the method of Rastelli.[10] Such intraventricular rerouting of left ventricular blood into the aorta, followed by a Rastelli procedure, is an alternative method of treating patients with a subaortic ventricular septal defect even in the absence of pulmonary stenosis because it obviates intraatrial rerouting and leaves the morphologic left ventricle as the systemic ventricle. Nevertheless, all of our patients have shown satisfactory progress in 1 to 2 years of follow-up and have no evidence of pulmonary vascular disease. One patient has evidence of aortic incompetence attributable to the repair.

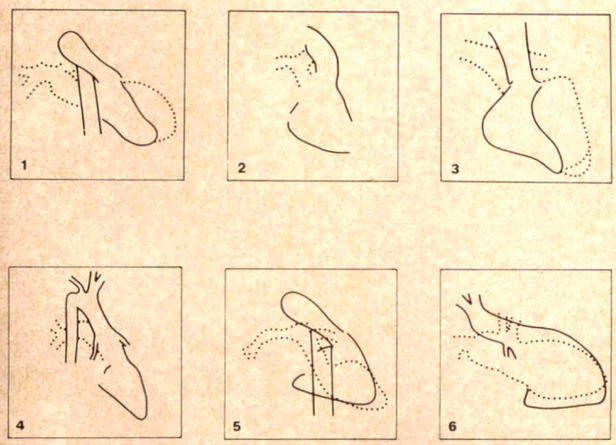

FIGURE 6. Superimposition of the outlines of the right ventricle and aorta **(solid line)** and left ventricle and main pulmonary artery **(dotted line)** obtained from synchronous angiocardiograms in Cases 1 to 6. The angiocardiograms of Cases 1, 4 and 6 are also illustrated in Figures 1, 3 and 5, respectively.

Morphologic Considerations

Our six patients have physiologically uncorrected transposition of the great vessels since transposition is associated with situs solitus of the atria and viscera and concordant atrioventricular relations. For most purposes the six cases are indistinguishable from cases of classically complete transposition. Paul et al.[1] indicated that in classic complete transposition with a *d*-bulboventricular loop the aortic valve is almost invariably higher and to the right of the pulmonary valve. In our cases, both angiocardiography and direct inspection at operation revealed the aorta to be located anteriorly and to the left of the pulmonary artery.

The "loop rule": Exceptions to the so-called loop rule of Van Praagh[11] have been documented, and it seems probable that they occur more frequently than suggested. Carr et al.[2] reviewed 109 consecutive biventricular biplane cardiac angiograms of patients with simple transposition of the great arteries with regard to the "predictive accuracy" of the "loop rule". They found that the prediction was correct in 69 percent and was incorrect in 17 percent; in 14 percent there was no prediction because the two great vessels were superimposed. According to the phase of the cardiac cycle, the relations were sometimes right to left, and sometimes left to right. Patients with pulmonary stenosis were excluded because Barcia et al.,[12] in 114 angiocardiographically documented cases of transposition of the great arteries, found 7 with slightly leftward displacement of the aorta. They classified these cases as *d*-transposition, because they believed that accompanying severe pulmonary stenosis was responsible for the clockwise rotation of the heart and angulation at the level of the stenosed pulmonary valve. Only one of our six patients (Case 4) had pulmonary stenosis; , it was moderate and required no surgical treatment. A similar proportion of patients with transposition whose anatomic features transgressed the "loop rule" was observed in a recent study at Killingbeck Hospital, Leeds, England.[13] Thus it is our opinion that there is a need to distinguish the *l*-positioned aorta from the *d*-positioned aorta in patients with "classically complete transposition." We suggest that this can be accomplished by referring to "complete *d*-transposition" or "complete *l*-transposition." However, it is necessary to expand this statement in terms of morphogenesis.

Morphogenesis: Contemporary opinion regarding the terminology and designation of various types of transposition and malposition of the great vessels in relation to the ventricles varies.[14,15] Several investigators have shown that a spectrum of cardiac anomalies exists between classically complete transposition and double outlet right ventricle with *d*-malposition,[16,17] and Kinsley et al.[18] have recently reported on the variety of positional anomalies of the conotruncus, stressing the classification and difficulties encountered in their surgical correction. The development of the conus is thought to play a part in the final interrelation of the great vessels and ventricles.[1,4,11,16,17] In complete *d*-transposition, with or without a ventricular septal de-

fect, a subaortic conus is normally present. However, in three of our cases, the conal septum was grossly deficient, so that the aortic valve ring approximated the pulmonary valve ring. This feature may have permitted the aortic valve to fall to the left and assume a position with partial overriding of the morphologic left ventricle. Indeed, this anomaly could be considered an intermediate form toward double outlet left ventricle. Nonetheless, this cannot be the full explanation of the *l*-transposed aorta because the ventricular septum was intact in our Cases 5 and 6. Equally, it is evident from our cases that the *l*-position is referable neither to pulmonary stenosis nor to scoliosis.[12]

It is possible that the levopositioned aorta is simply the result of additional conal rotation.[16] Nevertheless, the conal morphologic features in complete *l*-transposition are similar to those of the normal heart, except that the aorta and pulmonary artery are reversed. As such, the "straight septum hypothesis" promoted by Van Mierop and Wiglesworth[19] would serve to explain the arterial position. However, although the genesis of the anomaly remains equivocal, there is no doubt that these are cases of transposition. If one accepts the recent definition of Van Praagh[4] that transposition exists only when both arteries arise from separate morphologically inappropriate ventricles, and further accepts that this definition conveys no information concerning atrioventricular relations, then one can speak of complete *l*-transposition without fear of producing confusion.

Acknowledgment

We are grateful to all our colleagues at the Brompton Hospital who assisted in the diagnosis and management of the patients described herein. We are also grateful to Dr. F. J. Macartney, Killingbeck Hospital, Leeds, for permission to quote from work as yet unpublished; and we thank Miss C. Hunter for help in preparing the manuscript.

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Asymmetric Distribution of the Pulmonary Blood Flow Between the Right and Left Lungs in *d*-Transposition of the Great Arteries

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Pulmonary angiograms, radionuclide lung images and chest roentgenograms were evaluated regarding the incidence, magnitude and natural evolution of maldistribution of the pulmonary blood flow between the lungs in 63 patients with dextrotransposition of the great arteries. Approximately half of these patients had some degree of greater perfusion of the right relative to the left lung. A significant correlation was demonstrated between the incidence of this maldistribution of blood flow and the angulation between the main and the right pulmonary arteries. For any given angulation between these vessels, additional pulmonary stenosis increased the incidence of disparity in perfusion.

Our observations suggest the following developmental mechanisms: The maldistribution in flow results from the abnormal rightward inclination of the main pulmonary artery in the transposition malformation which straightens the flow axis from the main to the right pulmonary artery. Under these circumstances the momentum of the blood in the main pulmonary artery carries the blood preferentially into the right pulmonary artery. This momentum is increased when there is stenosis of the left ventricular outflow tract. Consequent differences in the mechanical properties of the two pulmonary vascular beds can increase this maldistribution. The disparity in perfusion between the lungs is not present in newborns with *d*-transposition, appears to be progressive in severity and in time may result in almost complete cessation of effective perfusion of the left lung. The effect of the Mustard operation on this abnormality of flow is discussed.

Unequal distribution of the pulmonary blood flow between the right and left lungs has been reported in a variety of congenital cardiac malformations even when unilateral pulmonary arterial branch stenosis or atresia is not present[1–12] (Table I). Several reports[10,12,13] have described relatively decreased blood flow to the left pulmonary artery in *d*-transposition of the great arteries. Because of these reports, we reviewed the roentgenographic, angiographic, hemodynamic and radionuclide lung imaging findings in all infants with *d*-transposition undergoing evaluation before corrective surgery. Our findings indicate a significantly greater frequency of abnormal distribution of pulmonary blood flow in patients with *d*-transposition than is implied by the paucity of published reports.

Material and Methods

Case material: Sixty-three patients with *d*-transposition of the great arteries had adequate angiograms of the pulmonary vascular bed for satisfactory qualitative analysis of the blood flow distribution between the right and left lungs and for an estimate of the relative blood flow velocity in each lung. This study was restricted to patients with normal visceral situs, concordant atrioventricular

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TABLE I

Reported Observations on Distribution of Pulmonary Blood Flow to the Right and Left Lungs in Patients With Congenital Heart Malformations

Author	Year	Diagnosis	Pulmonary Blood Flow	Method of Observation
Cleland et al.[1]	1957	*d*-TGA + PS	R>L	X-ray; angiography
Fleming[2]	1959	ASD	R>L	X-ray; bronchospirometry
Dollery et al.[3]	1961	PVS:ToF	L>R	$C^{15}O_2$ inhalation
Ellis et al.[4]	1962	*l*-TGA	R>L	X-ray; angiography
Garfunkel and Kirkpatrick[5]	1963	PDA	R>L	X-ray
Whitley et al.[6]	1963	PDA, VSD, ASD	R>L	X-ray; angiography
Wilson and Amplatz[7]	1967	ToF	R>L	X-ray; angiography
Friedman et al.[8]	1968	PDA	R>L	^{131}I-macroaggregated albumin
Chen et al.[9]	1969	PVS	L>R	X-ray; angiography; ^{131}I-macroaggregated albumin
Davies and Dow[10]	1971	*l*-TGA	R>L	^{131}I-macroaggregated albumin; angiography
Lin[11]	1971	ToF	R>L	^{131}I-macroaggregated albumin
Paul[12]	1971	*d*-TGA	R>L	X-ray; angiography; ^{113m}indium ferric hydroxide

ASD = atrial septal defect; *d*-TGA = dextrotransposition of the great arteries; L = left lung; *l*-TGA = levo-(corrected) transposition of great arteries; PDA = patent ductus arteriosus; PS = pulmonary stenosis; PVS = pulmonary valve stenosis; R = right lung; ToF = tetralogy of Fallot; VSD = ventricular septal defect.

(A-V) relation and *d*-transposition of the great arteries. Patients with associated single ventricle, double outlet right ventricle, persistent common A-V canal or atresia of a semilunar or A-V valve were not included. Infants with patent ductus arteriosus persistent after age 2 months were excluded because of the possibility that even a small patent ductus could significantly influence blood flow distribution between the two lungs. Patients with a partial venous switch operation (Baffes procedure), systemic to pulmonary artery anastomosis or pulmonary arterial banding were also excluded from this study because of the possibility of operatively induced abnormal distribution of the pulmonary blood flow.

The age of these patients ranged from 2 months to 3 years (mean 18.5 months) at the preoperative cardiac catheterization in which pulmonary blood flow distribution was analyzed. Observations made in infants younger than 2 months are not included in this overall analysis because of the possible persistence of patent ductus arteriosus. The angiographic observations in infants less than 2 months old and in 12 infants who had radionuclide lung imaging before the age of 2 months are considered in our study of the evolution of pulmonary perfusion patterns with age.

Fifteen patients were reevaluated after the Mustard operation to assess the effect of physiologic correction on the distribution of blood flow between the two lungs.

There were 59 infants with an intact ventricular septum or an anatomically small ventricular septal defect and four with a large ventricular septal defect. The pulmonary artery was entered in 62 patients, and both pulmonary arterial branches were explored in 27; in the others, the absence of branch stenosis was assessed with pulmonary venous wedge pressure determinations and angiography. Twenty-five patients with a peak systolic pressure difference of more than 20 mm Hg between the left ventricle and main pulmonary artery were considered to have significant pulmonary stenosis.

Methods: Pulmonary blood flow was estimated in most patients by the Fick method using measured oxygen consumption values according to the method of Wessel et al.[14]

Angiocardiography: All 63 patients had cut-film angiograms or 35 mm cineangiograms for assessment of the arterial and venous opacification pattern and the relative transit time of the contrast material in the two lungs. In most patients the contrast agent (Renovist® or Renografin®-76) was injected into the left ventricle rather than into the main pulmonary artery to avoid preferential delivery of the agent into either of the two branches. In patients with a large ventricular septal defect, however, the contrast material was generally injected into the main pulmonary artery just distal to the valve to avoid visualization of the aorta and the collateral pulmonary circulation.

The angiographic appearance of the pulmonary vascular bed in each lung was assessed and classified as (1) greatly diminished, (2) diminished, (3) normal, (4) increased or (5) greatly increased. The relative transit time of the contrast agent across the two lungs (time elapsed between injection of the contrast material and its appearance in the pulmonary veins) was assessed and classified as (1) equal in both lungs, (2) slightly delayed on one side, (3) moderately delayed on one side, (4) greatly delayed on one side and (5) with no visualization of pulmonary veins on one side. These two assessments were combined for an overall angiographic classification of pulmonary blood flow distribution between the two lungs (Fig. 1): N, normal or equal; 1+, slightly unequal; 2+, moderately unequal; and 3+, greatly unequal.

Radionuclide lung imaging: This procedure was performed in 31 patients. Radionuclide (iodine-131–macroaggregated albumin and technetium-99m-human albumin) microspheres were used. These particles were injected either into the left ventricle at the end of catheterization or into a peripheral vein subsequent to catheterization. Eight patients had injections at both sites approximately 24 hours apart. The following classification of the distribution of the radionuclide between the two lungs was used: N, normal (dominant side less than 55 percent); 1+, slight disparity (dominant side 56 to 65 percent); 2+, moderate disparity (dominant side 66 to 75 percent); 3+, great disparity (dominant side 76 percent or greater).

The chest roentgenograms were assessed in 56 patients regarding the pulmonary vascular markings in each lung, using the same classification as for the angiograms.

The results of angiographic, radionuclide and roentgenographic assessments were compared in each patient and a final category was assigned based on the method indicating the greatest degree of difference in pulmonary perfusion.

Results

An abnormal distribution of the pulmonary blood flow favoring the right lung was present in approxi-

mately half of the infants and children with *d*-transposition of the great arteries evaluated before corrective surgery (Table II). In no patient was the pulmonary blood flow judged to be greater in the left lung by the final combined assessment.

Selective left ventricular angiography and radionuclide lung imaging were judged equally sensitive in establishing the presence and assessing the degree of the disparity of perfusion of the right and left lungs. The chest roentgenogram was a less sensitive indicator, especially of lesser degrees of disparity.

Angulation between main and right pulmonary arteries: The distribution of the pulmonary blood flow between the two lungs was examined in relation to the angulation between the main and right pulmonary arteries. In the anteroposterior angiographic projection, three distinct configurations of the pulmonary artery and its bifurcation were recognized on the basis of this angulation (Fig. 2): a vertically arising main pulmonary artery with an angle of about 90° between the main and right pulmonary arteries (type A); moderate rightward inclination of the main pulmonary artery with an angle of approximately 120° (type B); marked rightward inclination of the main pulmonary artery resulting in an angle of about 135° (types C and D). In subtype D, there was frequent additional significant left ventricular

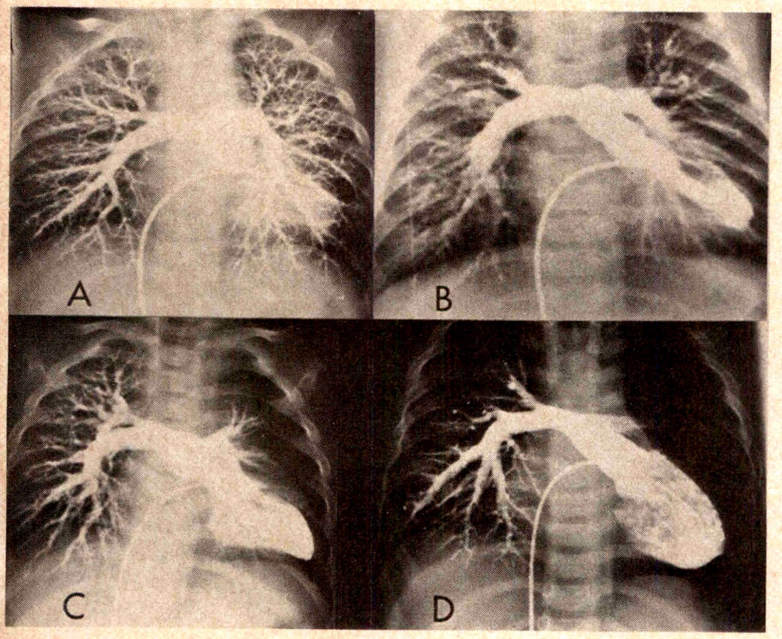

FIGURE 1. Pulmonary angiogram in *d*-transposition of the great arteries. **A,** normal right-left distribution of the pulmonary blood flow; **B, C,** and **D,** slightly, moderately and greatly unequal (preferential rightward) distribution, respectively.

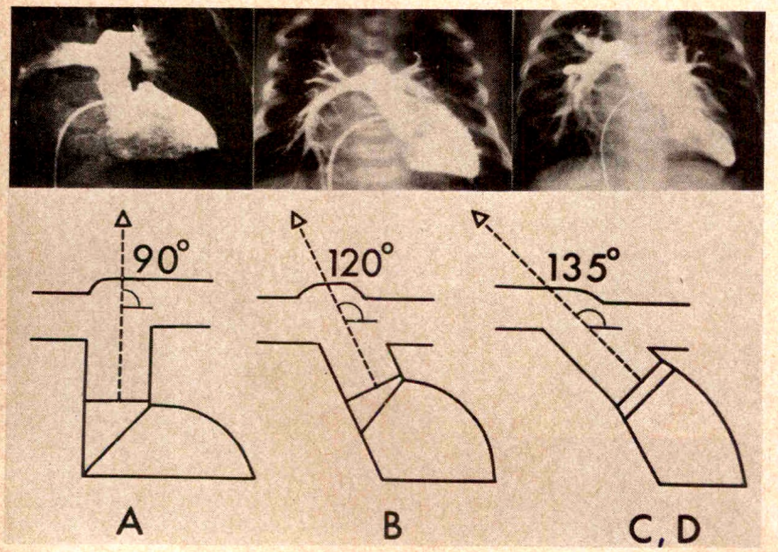

FIGURE 2. Angulation between the main and right pulmonary arteries in *d*-transposition. **A,** vertical main pulmonary artery with a 90° angle between the main and right pulmonary arteries; **B,** modest rightward inclination of the main pulmonary artery with an angle of approximately 120°; **C,** greater rightward inclination of the main pulmonary artery with an angle of approximately 135°; **D,** similar angle as in group C but with excessive subpulmonary conal tissue.

outflow tract obstruction due to a subpulmonary conus.

Of 18 patients who had a 90° angle between the main and right pulmonary arteries (type A), only 4 (22 percent) had a disparity in blood flow distribution, and in each the disparity was mild (1+) (Table III). However, when this angle was about 135° (types C and D), 14 of 19 patients (74 percent) had preferential distribution of pulmonary blood flow to the right lung and, in all but 1 patient, this disparity was moderate or great (2+, 3+).

Peak systolic pressure differences: The incidence of increased right pulmonary blood flow was also related to the presence of significant peak systolic pressure differences between the left ventricle and pulmonary artery (Table III). With each type of configuration (A to D), a larger proportion of patients with a peak systolic pressure difference of 20 mm Hg or more had increased right pulmonary blood flow by comparison with patients who had no such pressure differences. Of 62 patients, 25 had subpulmonary stenosis and 18 (72 percent) of these had an increased right pulmonary blood flow; in contrast, of 37 children without stenosis, only 14 (38 percent) had this disparity in perfusion.

Magnitude of pulmonary blood flow: To assess the effect of the magnitude of pulmonary blood flow on the disparity in perfusion of the two lungs, we studied patients with an abnormal angulation between the main and right pulmonary arteries (types B and C) but without left ventricular outflow tract stenosis. Whereas 9 of 16 patients (56 percent) with a pulmonary flow index greater than 5 liters/min per m^2 had preferential flow to the right lung, a comparable proportion of patients (5 of 10 [50 percent]) with an index smaller than 5 liters/min per m^2 also had this disparity. This finding suggested that there is no apparent correlation between magnitude of pulmonary blood flow and maldistribution of flow. However, since the flow index was calculated by the Fick method, some of the data, especially the higher flow values, may not be sufficiently reliable for such correlative analysis.

Radionuclide studies performed in 12 infants aged 5 to 60 days indicated relatively equal perfusion of the two lungs in all but 1 infant (Table IV). Nine of these infants had follow-up studies 5 to 35 months later, and in 5 perfusion of the right lung had increased by an average of 15 percent.

Illustrative case: The patient who first brought the pattern of abnormal distribution of pulmonary blood flow in transposition of the great arteries to our attention illustrates some previously undescribed aspects of pulmonary circulatory dynamics that can be associated with advanced degrees of maldistribution. In this patient, transposition of the great arteries with intact ventricular septum and small patent ductus arteriosus was diagnosed at the initial cardiac catheterization at age 5 days. The peak systolic left ventricular pressure was 27 mm Hg. The left ventricular angiogram (Fig. 3A) showed that the contrast material was distributed symmetrically to the two pulmonary arterial branches.

At the second cardiac catheterization at age 22 months, the peak systolic pressure was 36 mm Hg in the left ventricle and 12 mm Hg in the main pulmonary artery and both

TABLE II

Pulmonary Blood Flow Distribution to the Right and Left Lungs in 63 Cases of Dextrotransposition of the Great Arteries

Method of Observation	Total Cases (no.)	Pulmonary Blood Flow Distribution				
		Equal (no.)	Unequal no. %	Grade (no.) 1+	2+	3+
X-ray	56	33	23 (41)	16	6	1
Angiography	63	30	33 (52)	12	15	6
Radionuclide lung scan	31	16	15 (48)	5	5	5

TABLE III

Abnormal Right Dominant Distribution of Pulmonary Blood Flow as Related to Angulation Between Main and Right Pulmonary Arteries and Peak Systolic Pressure Difference (D) Between the Left Ventricle and Main Pulmonary Artery*

Pulmonary Blood Flow Distribution	MPA-RPA Angle						
	90° (A)		120° (B)		135° (C,D)		
	D<20	D>20	D<20	D>20	D<20	D>20	Total
R = L	9	5	9	2	5	0	30
R>L, 1+	2	2	3	4	0	1	12
R>L, 2+, 3+	0	0	4	3	5	8	20
Total	11	7	16	9	10	9	62

*Peak systolic pressure differences are expressed as mm Hg. Differences greater than 20 mm Hg were considered hemodynamically significant; L = left lung; MPA = main pulmonary artery; R = right lung; RPA = right pulmonary artery.

TABLE IV

Radionuclide Image Assessment of Pulmonary Blood Flow Distribution to the Right and Left Lungs in Dextrotransposition of the Great Arteries*

Case no.	Age (days)	PBF %R	PBF %L	Age (mo)	PBF %R	PBF %L
1	5	50	50	5†	73	27
2	7	51	49	10	54	46
3	8	53	47	—	—	—
4	11	47	53	27†	57	43
5	13	59	41	11†	77	23
6	26	54	46	5†	64	36
7	28	55	45	9	54	46
8	34	56	44	36	53	47
9	39	46	54	9	52	48
10	45	52	48	—	—	—
11	48	55	45	—	—	—
12	60	49	51	14†	62	38
Mean	27	52	48	12†	67†	33†
±SD		3.8	3.8			

*The studies were performed in 12 infants aged 5 to 60 days and repeated in 9 infants at ages 5 to 36 months.

†Data in second study revealed significant right dominant maldistribution of pulmonary blood flow.

L = left lung; PBF = pulmonary blood flow; R = right lung; SD = standard deviation.

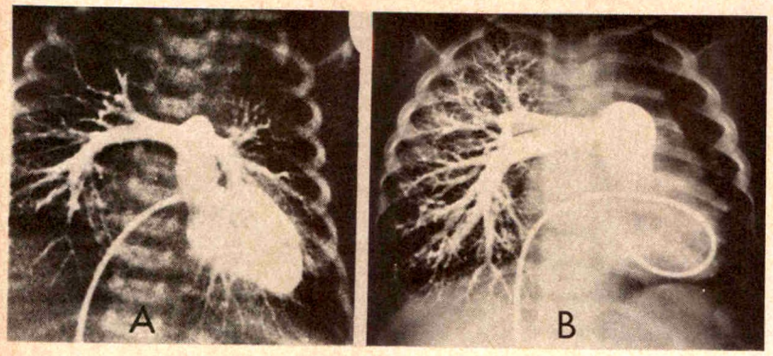

FIGURE 3. Illustrative case. Normal right-left distribution pattern in infant with *d*-transposition at 5 days **(A)**, and grossly abnormal right dominant pattern in same child at age 22 months **(B)**.

branches. Because the left ventricular angiogram (Fig. 3B) showed nearly total nonopacification of the left pulmonary arterial branches, thrombosis of the left pulmonary artery was suspected. Of the radionuclide microspheres injected into the left ventricle at cardiac catheterization 91 percent were distributed to the right and 9 percent to the left lung. A selective cineangiogram of the left pulmonary artery illustrated systolic filling of some small branches (Fig. 4A); however, during diastole (Fig. 4B), the contrast material returned in a retrograde direction to the main pulmonary artery and thereafter flowed into the right pulmonary artery. A selective cineangiogram of the descending aorta demonstrated prominent bronchial collateral circulation to the left lung with the contrast material flowing retrograde toward the main and right pulmonary arteries in a manner similar to that noted after selective left pulmonary arterial injection.

Corrective surgery (*Mustard procedure*) was carried out at age 26 months and the left pulmonary artery was found to be soft and apparently free of thrombosis. The left pulmonary venous orifices were smaller than the right orifices, presumably because of long-standing decreased pulmonary venous return from the left lung.

In a postoperative left ventricular angiogram 2 years later, the left pulmonary artery again did not opacify. Prominent bronchial collateral vessels provided the only blood flow to the peripheral left pulmonary artery from which retrograde diastolic flow into the main pulmonary artery was again observed.

Discussion

As early as 1957, Clèland et al.[1] pointed out that in patients with *d*-transposition of the great arteries, failure of the left pulmonary artery to visualize angiographically could not be interpreted as evidence of atresia or absence of this artery. They postulated that both the posterior position of the main pulmonary artery and the small size of the left branch were responsible for the poor visualization in the angiograms.

Davies and Dow[10] noted increased vascular markings in the right lung and a dilated right pulmonary artery in patients with corrected *l*-transposition of the great arteries and attributed these findings to a peculiar inclination of the pulmonary outflow tract and of the main pulmonary artery. Shaher et al.[15] suggested that the dilatation of the right pulmonary artery in *d*-transposition resulted from an alignment of the right and main pulmonary arteries and from a streaming or jetting of blood from the left ventricle in the direction of the right pulmonary arterial orifice.

Unilateral preferential pulmonary blood flow has been demonstrated in isolated pulmonary valve stenosis by Chen et al.[9] and in tetralogy of Fallot by Wilson and Amplatz.[7] Formation of a jet and an abnormal angulation between the main pulmonary artery and the two branches were considered responsible for the asymmetric distribution of the pulmonary blood flow in these lesions.

Findings in patients with maldistribution of pulmonary blood flow: In our patients with *d*-transposition, we found a large incidence of an exaggerated rightward inclination of the main pulmonary artery with a resulting increase of the angulation between the main and right pulmonary arteries (Fig. 2). There was a definite relation between the extent of preferential blood flow to the right lung and the degree of rightward inclination of the main pulmonary artery (Table III). Furthermore, for any given degree of rightward inclination of the main pulmonary artery, the incidence of perfusion disparity was increased when peak systolic pressure differences between the left ventricle and the main pulmonary artery exceeded 20 mm Hg.

In patients with extreme maldistribution of pulmonary blood flow, we observed an anomalous flow pattern in the pulmonary arteries. Although some forward systolic filling of larger left pulmonary arterial branches can be visualized with selective angiography (Fig. 4A), in cases with severely reduced left lung perfusion, we have observed diastolic reversal of flow in a retrograde direction from these branches toward the right pulmonary artery (Fig. 4B). This retrograde pattern of diastolic flow from the left pulmonary artery has also been observed when the contrast material enters through the bronchial collateral circulation or through a surgical anastomosis.

Maldistribution of the pulmonary blood flow in infants with *d*-transposition seems clearly age-related, and has not been observed with angiography in the neonatal period. The youngest infant in our study manifesting significant right-sided flow dominance in angiograms was 3 months old. Twelve neonates with *d*-transposition had radionuclide studies that confirmed the occurrence of essentially normal and equal distribution of pulmonary perfusion at this age (Table IV). Five of these infants manifested significant right-sided dominance 5 to 27 months later without any intervening surgery.

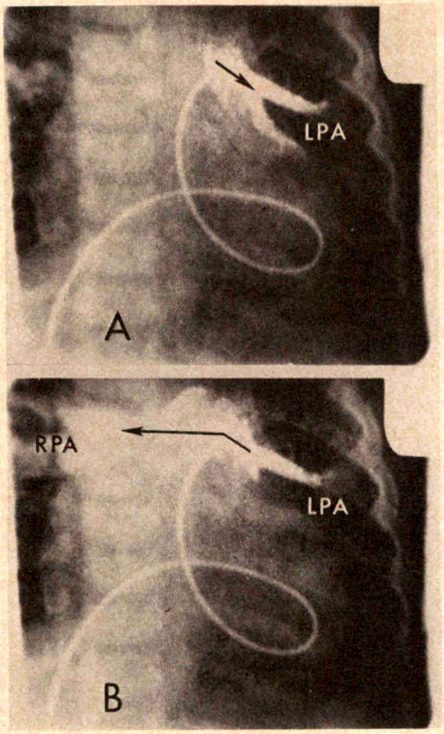

FIGURE 4. Same case as in Figure 3. Selective angiograms with injection into the left pulmonary artery (LPA) showing systolic filling **(A)** of several branches. During diastole **(B)**, the contrast material returns in a retrograde direction to the main and right pulmonary arteries (RPA).

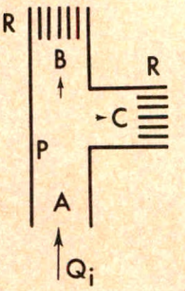

FIGURE 5. Model of a bifurcation to demonstrate the effect of the kinetic energy of the inflow (Q_i) into limb A on the distribution of flow to limbs B and C. P = pressure; R = resistance.

Hydraulic factors: When the angle between the main and right pulmonary arteries is increased and the flow axis straightened, the momentum of the blood in the main pulmonary artery carries the blood preferentially into the right pulmonary artery. An increased velocity of blood will enhance this momentum effect. Pulmonary stenosis as such increases the velocity of blood by jet formation, and an increase in left ventricular output can also result in a greater velocity of blood in the pulmonary artery if the pulmonary valve orifice or the pulmonary arterial lumen does not enlarge proportionately.

The effect of the momentum of the blood on the flow distribution at the bifurcation is illustrated with a simple inverted T-section model (Fig. 5); limb B is a direct extension of limb A, whereas limb C is perpendicular to limb A. Limbs B and C are terminated with equal resistances (R), and the inflow into limb A distributes into outflows through B and C. The pressure (P) would drive an equal flow through equal resistances (R), but the kinetic energy of the inflow favors flow in the straight direction toward B. The extent of the momentum effect depends on the relative proportions of the kinetic energy to the pressure (P). If the kinetic energy ($1/2\ \rho\ v^2$; in which ρ = density and v = velocity) is much smaller than the pressure, as a result of either low velocity or high pressure, the momentum effect will not be significantly operational in the model. An increase in velocity, decrease in pressure, or both, enhances the momentum effect.

Mechanical factors (pulmonary resistance and compliance): In addition to these local hydraulic factors in the main pulmonary artery and at the bifurcation, certain mechanical properties of the vascular bed in the two lungs, such as peripheral resistance and compliance, may greatly influence the distribution of blood flow between the two lungs.

The effect on flow distribution of the difference in mechanical properties of the two lungs is demonstrated with a mathematical model of the pulmonary circulation based on the Windkessel theory of Frank.[16] The left and the right pulmonary vascular beds are modeled with an elastic reservoir (Windkessel) terminated with a resistance. There is no inclination of the main pulmonary artery at the bifurcation (Fig. 6A). The systolic inflow into the main pulmonary artery (Q_i) is distributed into a right (Q_{Ri}) and left (Q_{Li}) pulmonary branch inflow. Part of this inflow passes through the resistances (R_R and R_L) during systole. Because of the compliance of the two vascular beds (C_R and C_L), part of the systolic inflow is stored and continues to flow through the resistances during diastole. The driving force for the diastolic flow is the energy stored in the distended elastic pulmonary arteries.

The pressure and flows are computed for a sinusoidal inflow (Q_i) during systole assuming an oscillatory steady state. The increase in volume of each reservoir (Windkessel) is assumed to be proportional to the increase in pressure (that is, V = CP, where V = volume, P = pressure and C = compliance) and the outflow through each resistance is assumed to be proportional to the pressure difference across the resistance (that is, P = RQ_0, where R = vascular resistance and Q_0 = outflow).

If the resistance and the compliance of the right and left vascular beds are equal, the flow distribution will be symmetric (Fig 6B, curve A). If the vascular resistance in the left lung exceeds that in the right and the compliance in both lungs remains equal, the systolic inflow into the left pulmonary artery will be reduced and there will be a relatively large diastolic retrograde flow (Fig. 6B, curve B). If there are both increased vascular resistance and reduced compliance in the left lung, the systolic inflow will be further reduced and the

diastolic retrograde flow will be smaller (Fig. 6B, curve C) since the less compliant vascular bed in the left lung cannot accommodate a significant systolic blood volume.

Abnormal developmental patterns with age: Our clinical observations and model analysis suggest the developmental mechanism outlined schematically in Figure 7.

In the normal neonate (Fig. 7, stage N), the pulmonary arterial pressure is initially increased, but decreases rapidly immediately after birth and more gradually later in the neonatal period. The pulmonary blood flow increases after ductal closure[17] and is distributed symmetrically between both lungs. Danilowicz et al.[18] demonstrated in the normal newborn infant and lamb that there is initially a marked disparity between the size of the pulmonary arterial trunk and the pulmonary arterial branches presumably due to bypassing of the right ventricular output during fetal life by the ductus arteriosus away from the lungs. After ductal closure, the pulmonary arterial branches enlarge gradually over several weeks and eventually the pulmonary vascular bed develops normally as a function of body growth and normal increase in the pulmonary blood flow.

In the neonate with d-*transposition,* the pulmonary blood flow is also distributed symmetrically between the two lungs (Table IV), even though many of these infants have significant rightward inclination of the main pulmonary artery (Fig. 7, stage 1). The momentum factors conducive to the development of preferential flow to the right lung are not yet effective since the kinetic energy of the blood in the main pulmonary artery is much smaller than the pressure. At this stage there is still increased pulmonary arterial pressure secondary to a thick-walled pulmonary vascular bed and relatively low flow velocity. After the early neonatal period, the pulmonary arterial pressure decreases to normal, the momentum effect becomes significant and, because of a favorable angulation, the blood flows preferentially into the right lung (Fig. 7, stage 2).

Graham et al.[19] and Keane et al.,[20] using angiographic methods, noted that in *d*-transposition and intact ventricular septum the left ventricular output appeared to be normal before age 3 months but appeared to be increased after age 6 months. Fisher et al.[21] observed that mild to moderate pressure differences between the left ventricle and main pulmonary artery often appear after the first few months of life and are frequently associated with formation of a fibromuscular ridge on the ventricular septum.

These two factors coming into play in early infancy can contribute to increased velocity of the left ventricular output. Since a definite relation between the incidence of maldistribution of pulmonary blood flow and left ventricular outflow stenosis could be demonstrated, and since we could find no conclusive evidence as to the effect of the pulmonary blood flow index based on the Fick method on this maldistribution, the increase of flow velocity as a result of pulmonary stenosis appears to be the more significant of these two factors.

Once the preferential flow distribution to the right is established, there is a greater stimulus for pulmonary vascular growth on the right whereas the left pulmonary vascular bed becomes relatively hypoplastic because of a smaller perfusion (Fig. 7, stage 3). Although the pressures in both pulmonary arterial branches are equal, the vascular resistance in the left lung is relatively

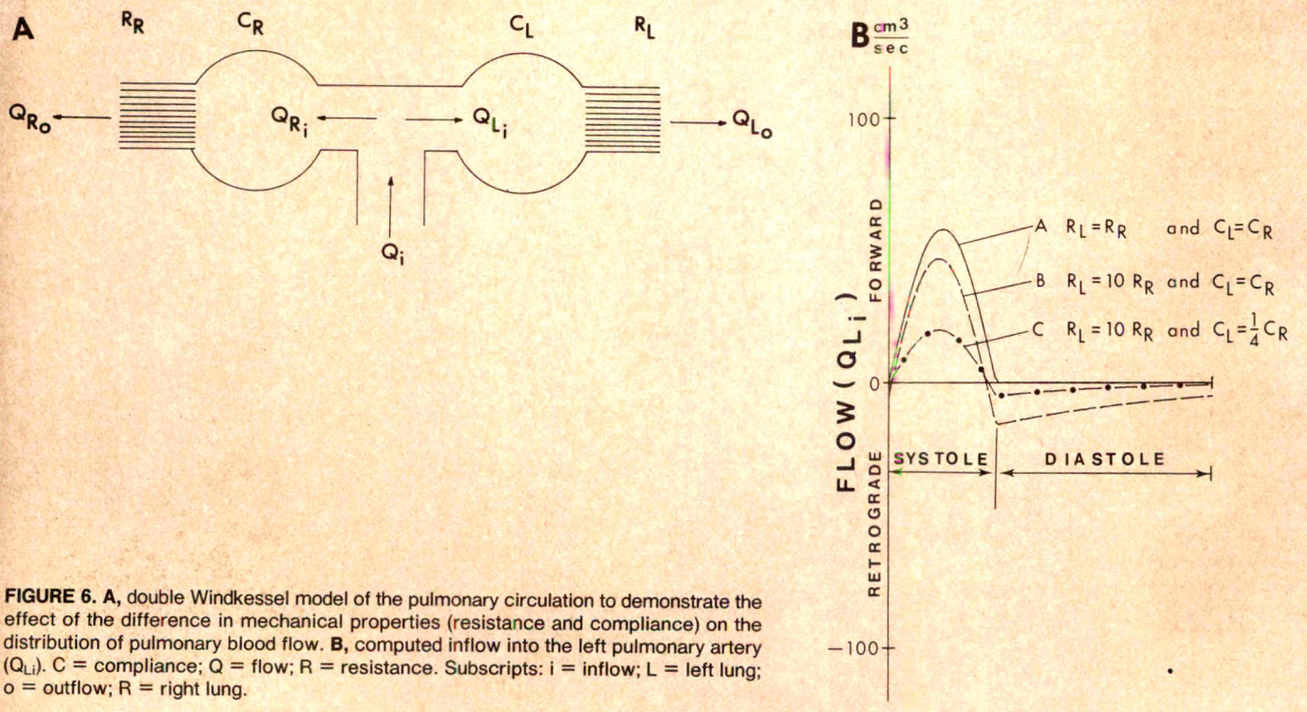

FIGURE 6. A, double Windkessel model of the pulmonary circulation to demonstrate the effect of the difference in mechanical properties (resistance and compliance) on the distribution of pulmonary blood flow. **B,** computed inflow into the left pulmonary artery (Q_{L_i}). C = compliance; Q = flow; R = resistance. Subscripts: i = inflow; L = left lung; o = outflow; R = right lung.

greater and the compliance of the hypoplastic left pulmonary vascular bed is relatively less than in the right. These differences in the mechanical properties of the two lungs, acting in addition to the momentum effect at the main pulmonary arterial bifurcation, contribute further to the disparity of lung perfusion.

The relative difference in vascular mechanical properties (resistance and compliance) between the right and the left lung appears to be progressive with age and, once hypoplasia of the entire left pulmonary vascular bed becomes marked, this maldistribution of flow will persist even if the abnormal angulation between the main and the right pulmonary artery is "normalized" (Fig. 7, stage 4). A shift of the mediastinum to the left as a result of a smaller left pulmonary vascular capacity can entirely eliminate the rightward inclination of the main pulmonary artery, yet the maldistribution persists presumably because of permanently altered mechanical properties of the vascular beds in the two lungs. At this stage the systolic filling of the left pulmonary artery is severely limited (Fig. 7, stage 4A), whereas during diastole (Fig. 7, stage 4B), retrograde flow from the left pulmonary artery occurs because of the relatively high resistance and the "Windkessel" effect. Flow to the left lung supplied by the bronchial collateral vessels or surgical systemic to pulmonary artery anastomoses also flows in a retrograde direction.

Radionuclide lung imaging: This procedure has proved particularly useful for quantitative and follow-up studies. In patients with *d*-transposition, the site of injection of radionuclide may affect significantly the distribution pattern between the lungs. When the injection is made into the systemic venous circulation, significant bronchial collateral circulation, often greater in the left lung, may alter the pulmonary distribution pattern of radionuclide. Under such circumstances, the radionuclide enters the pulmonary circulation through a dual pathway: (1) through an intracardiac right to left shunt and the pulmonary artery, and (2) through bronchial collateral vessels from the aorta. Injection of radionuclide into the left ventricle or pulmonary artery at cardiac catheterization excludes the bronchial circulation and for a given patient usually indicates a greater disparity of flow favoring the right lung than is

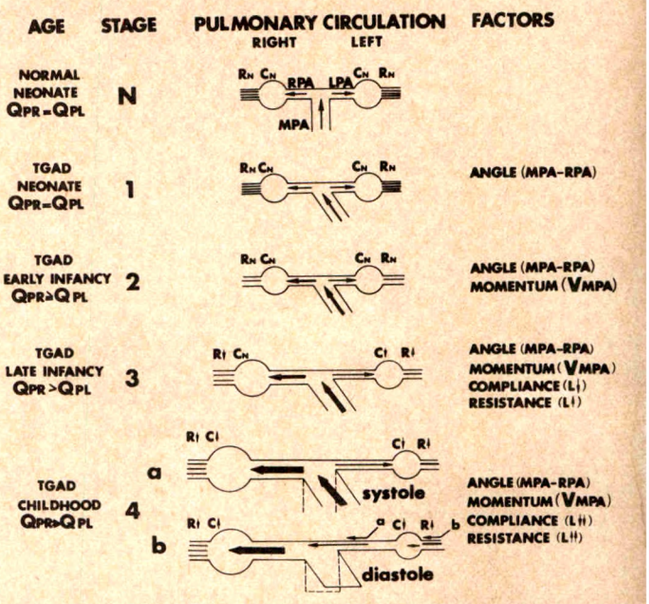

FIGURE 7. Anatomic and physiologic factors related to the development of an abnormal right dominant pulmonary blood flow pattern in *d*-transposition. a = proximal systemic-pulmonary shunt by way of surgical anastomosis into the left pulmonary artery; b = distal perfusion of the left pulmonary vascular bed by way of bronchial collateral vessels; C = compliance; L = left pulmonary vascular bed; MPA-RPA angle = angulation between the main and right pulmonary arteries; N = normal; Q_{PR}, Q_{PL} = pulmonary blood flow to the right and left lung, respectively; R = resistance; TGAD = *d*-transposition of the great arteries; ↑ = increased; ↓ = decreased.

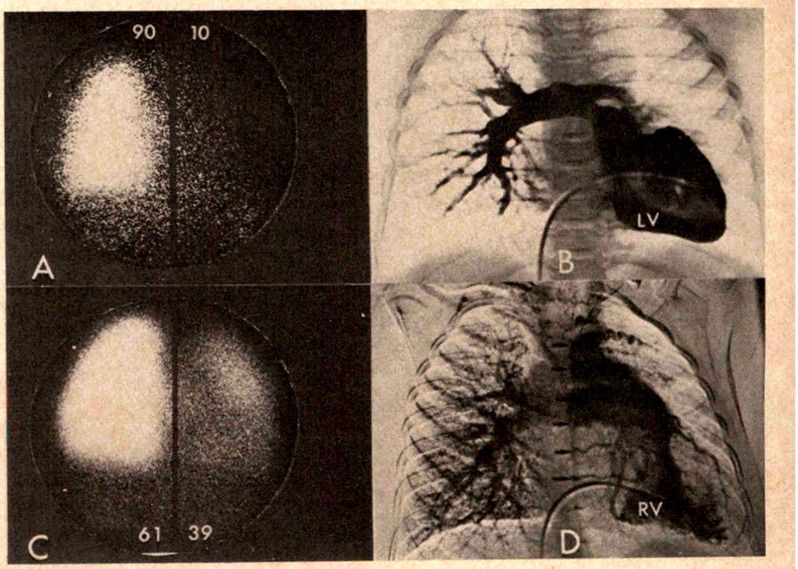

FIGURE 8. Radionuclide and angiographic studies of pulmonary perfusion in a patient with transposition, ventricular septal defect and pulmonary stenosis, illustrating contribution of bronchial collateral flow to left pulmonary vascular bed perfusion. **A,** lung image after injection of radionuclide into the main pulmonary artery (distribution 90 percent to the right lung, 10 percent to the left). **B,** angiogram with injection into the left ventricle (LV) indicating greatly diminished blood flow to the left lung. **C,** lung image after injection of radionuclide into a peripheral vein (distribution 61 percent to the right lung, 39 percent to the left). **D,** angiogram after injection into the right ventricle (RV) indicating prominent aortic collateral vessels to the left lung and massive opacification of the right pulmonary artery through the ventricular septal defect.

evident from the peripheral systemic venous injection (Fig. 8). In eight of our patients who were studied using both injection sites, the distribution to the left lung after the systemic venous injection was increased in amounts up to 24 percent (mean 8.1 percent) over the distribution measured by central pulmonary injection.

These technique-dependent differences of radionuclide distribution in *d*-transposition should be borne in mind when pre- and postoperative data are compared. After the Mustard operation, the systemic veins are directly connected to the pulmonary arterial circulation and the quantitative perfusion differences between venous and left ventricular or pulmonary arterial radionuclide injections noted preoperatively should no longer exist.

Effect of Mustard operation on pulmonary blood flow distribution: The question whether the Mustard operation will have an effect on the development of abnormal pulmonary blood flow distribution patterns in *d*-transposition deserves careful consideration. In assessing postoperative findings it is important to consider that available clinical evidence suggests that significant disparity in lung perfusion due solely to the main pulmonary artery to right pulmonary artery angulation mechanism is unlikely to develop after the 1st year of life. Progression of an initially mild subpulmonary stenosis, however, could be responsible for the delayed appearance of flow maldistribution either before or after operation. Morgan et al.[13] and Vidne et al.[22] reported the development or progression of preferential blood flow to the right lung after the Mustard operation. However, only one of the five patients of Morgan et al.[13] with postoperative abnormal pulmonary blood flow distribution had angiographic evidence of normal distribution shortly before the operation. In the study of Vidne et al.[22] peripheral venous injections were used both before and after operation and this factor alone could be responsible for an apparent increase in postoperative perfusion disparity.

Fifteen patients in our study had radionuclide lung imaging studies before and after the Mustard operation. In the 11 children who had pre- and postoperative peripheral venous injections only, there was no consistent postoperative change in the distribution pattern. Six patients had a small (mean 4.7 percent) decrease and five had a modest (mean 8.8 percent) increase in the left lung perfusion measured, but this postoperative increase on the left could be explained by the use of pre- and postoperative peripheral venous injection sites. The four patients with valid comparisons based on preoperative left ventricular radionuclide injections had no significant postoperative changes in pulmonary blood flow distribution. Furthermore, postoperative pulmonary angiograms in the entire group showed no overall changes in the distribution patterns.

Certain intracardiac surgical procedures, nevertheless, may influence the postoperative distribution of pulmonary blood flow: placement of an interatrial baffle so as to compromise either left or right pulmonary venous return, resection of subpulmonary or pulmonary stenosis and closure of a ventricular septal defect.

Clinical implications: The long-term implications of blood flow maldistribution between the two lungs in patients with *d*-transposition are only speculative. To date, we have been unable to attribute any clinical problems or symptoms to this pulmonary flow pattern after corrective surgery. Nevertheless, a marked decrease in effective perfusion of an entire lung such as that observed in advanced cases cannot be considered insignificant. In the left pulmonary vascular bed, thrombotic changes may occur because of a local sluggish circulation, especially preoperatively when polycythemia is commonly present. In the right lung, however, pulmonary vascular obstructive changes may develop because of a persistently increased pulmonary blood flow.

Further investigations are needed to determine whether the Mustard operation performed early, perhaps before age 6 months, could prevent the development of abnormal distribution of pulmonary blood flow. Although the main pulmonary artery to right pulmonary artery angulation, which we consider a principal factor responsible for flow maldistribution in *d*-transposition, remains unaffected by this operation, correction of the physiologic features of transposition may have a significant bearing on the evolution of the perfusion abnormality. Early physiologic correction normalizes the increased pulmonary blood flow in *d*-transposition of the great arteries, and resection of significant pulmonary stenosis decreases the blood velocity and momentum in the pulmonary artery. These changes in hemodynamics may be sufficient to prevent progression from stage 1 to stage 3 (Fig. 7). Furthermore, early perfusion of the coronary arteries with fully oxygenated arterial blood may prevent or reverse right ventricular dysfunction,[23] reduce the posterior bulging of the ventricular septum into the left ventricle and thus arrest the progression of left ventricular outflow tract stenosis, a factor in causing increased velocity and momentum of flow in the pulmonary artery.

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REVIEW

Limitations of the Computer in Electrocardiographic Interpretation

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Use of the computer for electrocardiographic interpretation has steadily increased over the past decade. Although acceptance by a majority of physicians has been slower than originally anticipated, it now appears assured. Nevertheless, the approach has limitations. These are primarily a result of the lack of objectivity in clinical electrocardiographic criteria for both measurement and diagnosis. The limitations are best judged by reviewing experience with a variety of programs. Currently this still involves abstracting from the reports of developers. Although not all developers have analyzed every portion of their programs, in general the data from one program apply to others; that is, all are with minor exceptions at the same "state of the art." Awareness of the limits of computer performance allows a physician to use the computer properly in his current electrocardiographic practice.

Frost and Sullivan, Inc.,[1] a concern that studies markets and makes forecasts, has predicted that by 1980 more than 100 million electrocardiograms will be obtained with computer assistance. They have stated: "To perform these services, $220 million worth of computer systems and $135 million of related terminals will be purchased; the annual expenditure on these experiments by 1980 will be $70 million and $150 million, respectively. Supplies, maintenance and related services may reach $40 million, and processing services using time-shared facilities or regional operations are conservatively estimated at $350 million. The federal government has already invested more than $11 million in bringing [computer-assisted electrocardiograms] from the laboratory to community service." This concern has concluded that computer-assisted medical interpretative systems can now be made available to the primary care physician and has reported that responses to questionnaire surveys indicate that 78 percent of physicians are in favor of having computer-assisted electrocardiograms and other computer-assisted interpretations.

From the physician's view this means there is an immediate need to evaluate the current status of computer electrocardiography. Electrocardiography led the way in bringing automation to data obtained directly from the patient. For this reason significantly more has been published regarding computer use in this field than in others, and it is thus a good model to review. In fact, as other areas in cardiology begin to use computers, essentially the same research, developmental, implementation, evaluatory patterns and errors are being repeated.

Available Computer Programs

At least 50 groups in the United States now provide partial or completely automated electrocardiographic processing on a supplier basis to providers of care. There are numerous claims concerning the diagnostic capability, accuracy and reliability of these programs. Conferences on computer electrocardiographic processing have generated questions as well as clarification. Some have called for "certified" programs. But today this term means only that a program has been adapted for use in a specific computer; it does not refer to diagnostic accuracy as such.

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Availability of easily applied performance standards would be a panacea. But, in the past most designers of electrocardiographic programs had to devise their own tests of diagnostic capability. Interestingly, this has resulted in generally similar statistics for each new program developed. Helppi et al.[2] suggest applying rigorous performance specifications for measurement programs and restricted specifications for the interpretative programs. They suggest that reports about the performance of computer programs be discontinued until more objective evaluation procedures are developed. However, in view of the differing characteristics of the various programs, the best evaluation for the next decade may simply be to test that the program does what its developers' specifications claim it does.

Milliken et al.[3–9] have described and evaluated experience with the typical hospital-based computer system for analysis of standard 12 lead electrocardiograms. The difficulties encountered included lack of reliability of P wave recognition, distortion secondary to background noise and baseline drift and other technical imperfections. They draw attention to a necessary distinction between computer programs utilizing binary logic and decision tables and those employing multivariate statistical analysis. They have discussed the characteristics of several available electrocardiographic terminals and recognize their contribution to the overall system. They found that agreement between electrocardiographer and computer ranged from 70 to 90 percent for electrocardiograms identified as normal. For tracings with evidence of serious abnormality (myocardial infarcts, left ventricular hypertrophy and conduction defects) agreement ranged from approximately 75 to 85 percent. Sixty-six percent of tracings with rhythm disturbances were correctly interpreted.

Many of the pioneer programs were copied, some with authorized and some with unauthorized modifications. Some programs, copied and "improved" by persons without sufficient knowledge and background, have yielded poor results. Whenever a program's results differ too much from those expected, one reason may be inappropriate adherence to the designer's specifications.

The program evaluated most often, by various methods, is that developed at the Medical Systems Development Laboratory (MSDL) of the U.S. Public Health Service. Because of the long public history[10–15] and use of this program, it is helpful to concentrate on it as an example and to note the variety of evaluations possible (measurements, repeatability, noise, comparison, predictability, among others). All assessments must be performed using data obtained from instruments and systems that conform to the specifications of the designers. It should be emphasized that the MSDL program is part of a total electrocardiographic processing hardware and software system whereas some other systems focus only on the programs themselves.

The MSDL System

Wave form measurements: The developers of the Medical Systems Development Laboratory (MSDL) were the first to publish extensive data and methods for evaluation as part of a series of progress reports.[16–24] The first published evaluations in the 1960's concerned wave form measurements only. The published tolerances for wave measurements showed that small waves of 0.025 to 0.06 mv gave the computer program major difficulty, as they still do for most on-line programs. There was also a variable error factor due to difficulty in ascertaining the onset or offset of waves with a gradual rate of change in slope. This indicated early that diagnosis ultimately dependent on small wave forms would be most prone to error (for example, a false negative result could be obtained in tracings in which a small R wave preceding an S wave seemed to nullify a diagnosis of diaphragmatic infarct or in which a small Q wave preceding an R wave as in leads V2 and V3 suggests an anterior infarct). Overall, analysis of nonzero or nonsuppressed wave forms (P ± 0.025 mv, Q 0.03 mv, R 0.05 mv, S 0.06 mv, T ± 0.03 mv) demonstrated that 97.3 percent of these wave forms were suitable for use in evaluation.

Dobrow et al.[20] and others published detailed tables of the correspondence between measurements made by physicians and the computer program. Agreement ranged from 39.7 to 100 percent depending, as could be predicted, on the amplitude, duration and slope of a wave form. The physician also evaluates wave form patterns on the basis of width, amplitude and slope. This may explain, as Dobrow's studies also show, why some wave forms found by the computer were found by the physician only on second review. In some instances, of course, waves were not present (computer error) or were not found by the computer because of the tolerances noted earlier.

Repeatability of wave form measurement was also tested early. Repeatability must be evaluated on the basis not only of the repeated presence of the wave form but also of the repeated presence of its characteristic features. Standard deviations ranged from 0 to 0.493, depending on specific wave form height and amplitude. In the MSDL program, 94 percent of measurements were repeatable within what were judged to be suitable limits. Travis[25] did a reproducibility study of this program by playing back electrocardiographic analog tapes five times to determine whether this procedure significantly altered computer diagnosis. He found agreement rates of 92 and 98 percent for normal and abnormal tracings, respectively; in addition, 96 percent of the diagnoses were in agreement with each other on playback. Travis noted, however, that there are significant problems in playback of analog tapes. The playback tape head may not be aligned with the recorder; there is always "flutter" in any tape deck; the tape stretches; and, as it is redigitized, the same point is not reproduced so that there are always minor differences in each new digitized version and new noise levels that will affect the computer's response to the data.

Noise levels: Although superficially it might seem otherwise, on-line telephone transmission of electrocardiograms to a computer is generally less noisy and better than intermediate tape storage.[26] This point should be borne in mind when necessary economic tradeoffs are made by those concerned with tape recording and processing. Nevertheless, it is possible to obtain satisfactory, if not ideal, results when the tape equipment meets the required specifications for the program in use. Meeting such specifications, of course, may add to the cost of tape use.

Noise levels of 25 μv or more make a tracing unsatisfactory.[27] Most of the early computer programs were

developed before recommended specifications for equipment had been made and they relied on analog or digital filtering of wave forms to simulate the tracings on the single channel electrocardiographs of the era. Most systems today still do not comply with ideal specifications because of practical cost considerations. But details of hardware noise in today's mass-produced commercial systems generally need not concern the user, as was the case in earlier days.

Comparison with Mayo Vector 1968 system: Fleischli et al.[28] were the first group to compare two computer programs.[28] Such comparisons can resemble a comparison of apples and pears unless the recommended equipment is used for each program. Fleischli et al. followed the correct procedure. Because each program studied was developed for different equipment and with different criteria the differences were expected to nullify declarations that one program was better than the other. Their study thus yielded a comparison of results obtained with a scalar system (MSDL), a vector system (Mayo), interpretation by a cardiologist and utilization of the criteria of a physician team when reasonably identical tracings were presented (two sequential electrocardiograms were obtained from each subject one for each computer). One of the earlier MSDL standard scalar systems (Version B) was compared with the Mayo Vector 1968 system. Compared with physician assessment, both programs had a greater incidence of abnormal interpretations. This is always to be expected because current computers must follow criteria, as specified, all of the time. Indeed, a program with few "false positives" is probably following inadequately rigid criteria. Tracings in this study were read by (1) a team of physicians with varied training (internship to board eligibility), and (2) a practicing electrocardiographer. (Fleischli et al. concluded, as others have in different fields, that after a point length of training contributes little to an individual physician's overall results.) Observer variability within the physician group was 31 percent, a finding representative of the usual observer variability.

The authors tabulated false positives and false negatives according to whether or not three of the four elements in the test (cardiologist, three physicians, scalar system, vector system) were in agreement. When three systems agreed, the system in disagreement was considered to have made either a false positive or a false negative interpretation. There was consensus regarding 64 diagnoses in the 781 electrocardiograms obtained from a relatively normal ambulatory university faculty population. The cardiologist had 168 false positive and 54 false negative interpretations, the vector system 284 false positives and 23 false negatives, the physician team 26 false positives and 20 false negatives, and the scalar system 374 false positives but only 4 false negatives.

From the standpoint of preventive medicine, the crucial aim is to obtain the fewest number of false negatives because missing a positive case generally has the most detrimental effect on the patient's well-being and cost. In effect, 6 percent of positive cases were missed by the scalar system, 31 percent by the physician team, 35 percent by the vector system and 84 percent by the electrocardiographer (primarily because of his diagnostic criteria for left ventricular hypertrophy). It would appear that both computer programs did well in relation to false negatives. But a physician using a computer system as an aid should be prepared to expect "false positives," although in fewer numbers than with the pioneer programs.

Comparison with 1971 IBM program: Recently a researcher-academician team from the National Institutes of Health[29–31] evaluated the International Business Machines program of 1971 and contrasted the experimental version of that now commercially available program with the MSDL Version D and Mayo 1968 programs. The researchers proposed their own methodology for evaluation as being without pitfall since they believed that the reliability of electrocardiographic computer programs "has never been adequately evaluated." Such attitudes impose grave limitations on computer use, particularly when studies are developed with the aim of evaluating specific commercially available programs. Predictably, when a method that "avoids the pitfalls of previous studies" is used with a program for which it was designed, that program does best. In the evaluation, computer processing for the IBM program was performed at IBM facilities, thus using the recommended equipment and methods of the manufacturer-developer. Processing for the other two programs was performed at the researchers' site without necessarily following or obtaining the appropriate recommendations regarding equipment or type of signals needed. As noted earlier, this can lead to erroneous judgment.

In the IBM-NIH evaluation the physician readers studied were required to use specified criteria. Some of those criteria (those for hypertrophy, for example) were developed after both the MSDL and Mayo programs had been developed. The practice of comparing a computer program that has known predefined criteria with a program that has known different criteria cannot be recommended unless one wishes, for the sake of statistics, to document differences known in advance. This can be done more easily by evaluating the criteria without the expense of a computer run. Of course, if one is not doing an evaluation but is developing a program the approach makes more sense.

In developing usable criteria for a computer program one must initially select some set of criteria from an accepted source as a base and then adjust it by trial and error to the precision and requirements of a computer program; a tuning results. The NIH studies can be said to have been part of the routine for improving the criteria for a specific program. The evaluation data in effect became part of the program's redesign.

In reviewing evaluations, it is helpful to distinguish between a true evaluation and a progress report. Experience with the design of computer programs has shown that a true impartial evaluation can be expected only from those not contributing to improvement during

the development process. Like most other developers, I have been well aware of this fact and have learned that evaluations are of most value when they stem either from continued clinical use by those not part of the design process or from rejection by clinical users.

Overall performance for the IBM-NIH–evaluated program showed agreement between physician reader and computer in 75.5 percent of tracings. Disagreements (20 percent) were due to differences in criteria. (These variations have been reduced in the currently available commercial version.) Four percent of disagreements were due to program errors. These data are essentially the same as those found by others in initial evaluations of their own programs using their own original equipment and specifications.

Use of the NIH technique designed for the IBM program, yielded more physician-computer differences and more program errors for the MSDL Version D and the Mayo 1968 versions. The errors in the MSDL program had previously been documented by the developers and the government had issued a contract for improvements that have since been made. However, it is important to understand why differences in evaluations occur. Part of the difference in results in the NIH study is explainable by the higher frequency response in the data used and the nonrecommended equipment used at NIH. The practitioner must be aware that, like drugs, computer programs must be used as directed if reproducible results are desired. A nonclinical researcher may be less aware of this basic fact, thus one should be wary of data obtained when clinical products are evaluated in a nonclinical environment.

Clinical evaluation of MSDL program: The clinical value of the MSDL electrocardiographic program and system is best shown by overall results such as those cited by Neufeld et al.,[32,33] who used the early Version B. They reported electrocardiographic data accumulated during a long-term epidemiologic survey of ischemic heart disease in Israel in men over age 40 years; the study included 12 lead electrocardiograms recorded on magnetic tape and processed by MSDL in Washington, D.C. They concluded that computer reproducibility was superior to that of expert electrocardiographers. They suggested that tracings identified as normal by the computer may be accepted as such; those regarded as abnormal require physician validation. They also suggested that the magnetic tape electrocardiogram has greater sensitivity than the conventional paper recording and that abnormalities detected in the former may be clinically significant.

Of more significance, Neufeld et al. were the first to show the value of computer electrocardiograms in predicting disease. The computer's initial interpretation of tracings indicated a 26 percent incidence rate of ischemic heart disease in the population, a rate far higher than that indicated by human readers. A 5-year follow-up of patients with tracings classified as indicating infarct by computer but not by cardiologists revealed a very high predictive value for the forms. Thus in many cases the computer results were not false positive but prepositive. This early study suggests that one should take great care before dismissing a "false positive" computer diagnosis.

Craig and Derryberry[34] reported good results with the MSDL program as a screening tool in occupational medicine. Acker et al.,[35] in a nearby center, described limitations in clinical use of the program. A U. S. Health, Education and Welfare Department publication[15] discussed in more detail clinical application of the program in community hospitals with predominantly abnormal tracings, using the MSDL Version D with modifications. Elliot and Simmons[36,37] noted that physician readers did not amend computer assessment in 41 percent of instances. Lack of arrhythmia classification was not the major factor in instances of computer-physician disagreement and was not a drawback. There was minor amendment 43 percent of the time and major amendment 16 percent of the time.

The usual areas of amendments were: ST-T segment (27 percent); atrial and ventricular arrhythmias (15 percent); atrial abnormalities (11 percent); Q-T measurements (11 percent); old anterior and inferior infarcts (9 percent); left axis deviation (6 percent); left ventricular hypertrophy (6 percent); and other (15 percent). Seventy-five percent of these differences were due to disagreement among criteria. It is difficult to resolve criteria differences as such. Often these stem from judgments of measurements that may or may not have been properly made by the computer.

Current state of the MSDL program: Program variations or new designs have been used in several nationwide processing service organizations and by several American and foreign groups. The current status of the MSDL electrocardiographic programs can be considered in the light of recent developments. The government has sponsored development of a new Version E, whose evaluation may be expected in late 1975–76 to show improvements in certain areas of measurement and diagnosis (Version D, with a variety of user site-specific specifications is now most commonly used). Preliminary data in this evaluation have produced clear documentation of why the cardiologist is a difficult "standard" and why the disease correlation approach, in the long-term, is useful to pursue. In this study, four senior cardiologists, three hospital electrocardiographic readers and Versions D and E of the program are compared. When there has been consensus among three of the four senior cardiologists, their false positive interpretations range from 21 to 76 percent and their false negative interpretations from 5 to 62 percent. Early review of the data shows that the evaluation of the computer results can change by omission of any one specific cardiologist as standard. Interestingly, the data suggest that if a group is left out as part of the "consensus standard" (in this study the hospital readers and the computer program's criteria) then their results appear to be relatively worse than those of groups whose data were included in the standard consensus data. No evaluation of Versions D and E has yet been available, in part because of this real difficulty.

New user-oriented program: A new program by some of the MSDL developers, patterned after the concepts of the first system, still follows some of the MSDL time-tested subroutines but now is part of a hardware system based on the MSDL dedicated computer concept.[38] Firuglio et al.[39] report 98.5 percent agreement on normal tracings and 82.5 percent agreement on abnormal tracings in initial use. The Hewlett Packard Company has added several features in areas of electrocardiographic record keeping and updating to this new program, which has user orientation as its basic premise, allowing changes in diagnostic statements to be made with relative ease.

Washington, D. C. VA Hospital Program

The D. C. Veterans Administration Hospital electrocardiographic programs have been spearheaded by Pipberger, whose underlying aim in computer use has been improvement of electrocardiographic diagnosis. He has been the leading American advocate for the Frank "orthogonal" lead system. Indeed, without his continuing emphasis on that system, its use might have been less widespread.

Borun et al.,[40] using a modification of this electrocardiographic computer program, compared visually determined 12 lead abnormalities with those in the Frank 3 lead system. The latter identified most standard lead electrocardiographic abnormalities. However the authors concluded that further study would be necessary to determine whether the Frank leads had a higher sensitivity or lower specificity.

The first technique for sampling electrocardiographic data and preparing it for input into a computer was developed for this program.[41–44] Programs to measure and interpret the data were then developed and reported for analysis of orthogonal leads. The early work by the Pipberger group[45–49] referred to methodology. However, their more significant reports[50–56] have demonstrated what can be achieved through computer analysis. A multiplicity of heretofore poorly defined or unknown electrocardiographic and clinical relations have been established. These have related, for example, to changes in the electrocardiogram due to cardiac enlargement, differentiation of ventricular hypertrophy or infarcts through use of statistical algorithms. This research differentiates Pipberger's group from others and also indicates the utility and flexibility of the computer programs used.

In view of the basic research interest, the limitations of the Washington Veterans Administration programs have not had to be documented to any great extent by the developers. Cornfield et al.[57] have stated that the program is 69 percent accurate in classifying patients on the basis of known clinical conditions. Although their figure refers only to specific conditions tested, it is highly significant in that it reflects agreement not with cardiologists but with a diagnosis diagnosis derived from other sources.

There is relatively little routine clinical use of this program, because the program output is extensive in detail and oriented to research. Howevever, such use is increasing in some areas now that the basic electrocardiographic program is available on the same commercial hardware system that provides the new Hewlett Packard/Clinical Systems Associates program noted previously.[38]

I believe that Pipberger's major (and commendable) effort has been to arrive at a method by which computers and computer programs can be used to produce clinically accurate answers, not just the answers of an electrocardiographer. The limitation of this approach is obvious; it is a time-consuming process to verify the disease suggested by existing (or new) electrocardiographic criteria. This effort is necessary, however, if we wish to lessen the known error due to variability among cardiologists. Pipberger's point has been that electrocardiographic criteria should be made on other than a cardiologist's impression of what an electrocardiogram means, and in that he is correct. His use of conventional and new statistics can serve as a model.[57,58–60] Of course, until we have clearly defined electrocardiographic means for identifying disease (which may be decades away), a feasible approach appears to be to keep reformulating criteria, when possible, on the basis of work such as that from the Washington, D. C. Veterans Administration and have computer programs follow it. Cardiologists can then first consider the possibility that the computer is correct, that is, use the computer as an aid, always being aware of the intrinsic limitations in reference to diagnostic accuracy and precision. Pipberger and Cornfield's recent writings[61,62] on computer program selection and evaluation have urged careful analysis of both programs and evaluators.

Mayo Programs

The first Mayo program available was a 1968 version. Data on it from its developers were sparse.[63,64] A new version, introduced in 1974,[65] is greatly reworked and improved. The early Mayo program had widespread circulation without the benefit of the environment in which its use was intended. Such use can (and did) result in significant misunderstandings of the program's purpose and value.

The various Mayo programs use X, Y and Z leads as well as a rhythm strip. All electrocardiograms with noise are rejected by a human monitor. The system is utilized at the Mayo Clinic in more than 90 percent of cases. Since recordings have also been made and analyzed in neonates and children, the pediatric experience with this program appears to be greater than with other programs.[66,67]

In one study of 6,000 electrocardiograms obtained with this system in 24 days, Smith[69] found measurement errors in 4 percent. These errors did not necessarily produce diagnostic error, a fact that applies to all computer programs. The computer can compensate for errors, and most programs have the logic to consider alternative data for many diagnoses.

In the Mayo program, P waves are missed and are a source of problems in about 1 of 60 electrocardiograms. Perhaps this is a lower problem rate than that of the physician. R onset logic has been developed using both difference functions and spatial vector resolutions.

Pacemakers are handled by examining the raw data for spikes. Other program developments are in progress including pathologic and physiologic correlation data. Smith[68] has summarized the early results (Table I). Of abnormal evaluations by the computer, 2,139 were identical with the physician's assessment, 409 were overcalled, 167 were missed and 72 were both missed and overcalled.

Clinical evaluations: Bertrand and Duffey[69] of IBM have used electrocardiograms in an employee health testing program. Their use of the 1968 Mayo Clinic program represents an evaluation of a computer electrocardiographic program in an industrial clinic setting. Overall, the population consisted of 83 percent normal, 7 percent borderline and 10 percent abnormal subjects. More than 23,000 computer electrocardiograms have been reviewed, and the results of an analysis of 1,000 have been reported. The computer agreed with the cardiologist in 677 normal and 84 abnormal cases, and disagreed in 47 normal and 192 abnormal cases. There was overall agreement of 93.5 percent in the normal cases and 30 percent agreement in the abnormal cases. Noise accounted for 3 to 7 percent, respectively, of the disagreements in each group. In the normal cases, the most commonly missed diagnoses were right bundle branch block, T wave changes and S-T segment displacement, followed by infarction and other less significant diagnoses. The evaluation criteria were severe. Even one incorrect statement among several correct statements in an interpretation was classified as a disagreement with the computer on the entire electrocardiogram.

Some interesting heart rate results reported by Bertrand and Duffey show how the computer may add precision to our usual criteria. In 12,000 electrocardiograms the mean and median heart rates after the patient had been supine for 15 minutes were, respectively, 65 and 64 beats/min (range 48 to 87). This finding confirms the suggestions of others using computers that a cutoff of 60 beats/min to designate bradycardia may not serve a useful clinical purpose. A level of 50 beats/min would include only 5.7 percent of the population rather than the overly high 36 percent at the rate of 60 beats/min. Similarly, 99 percent of the population has a heart rate of less than 95 beats/min. Therefore, a level of 100 beats/min for tachycardia, which picks up only 0.27 percent of the population, may not call attention to subjects who may need greater surveillance.

The satisfactory results obtained with the Mayo program at the designer's heart station at the Mayo Clinic over many years contrasts with often cited evaluations of the program, such as that by Bruce and Yarnell.[70] This group analyzed 373 cases. The computer was judged correct in 91 percent of its normal assessments and in 47 percent of its abnormal assessments. There were false positives in 53 percent of the cases interpreted as abnormal and misclassified cases in more than 25 percent. In a further test, in which 165 random recordings were repeated almost immediately, with no change in electrode placement, the computer significantly altered its interpretation 31 percent of the time. Bruce and Yarnell concluded that the risk of error when

TABLE I

Physician Versus Computer Assessment of Electrocardiogram in Mayo Program*

	Normal by Computer	Abnormal by Computer	Total
Normal by MD	3163	181	3344
Abnormal by MD	31	2787	2818
Total	3194	2968	6162

*Data from Smith.[68]

a healthy person with a normal cardiogram is screened by the program is so great that clinician review of every report is essential. By contrast, Guller et al.[66,67] using the Mayo three lead orthogonal program with newborns, found advantages. No special precautions were used in using the vector program in this difficult age range, and no specific problems were reported in a series of 100. It would appear that those who understand that computer programs are to be used as an aid can make excellent use of them in performing difficult tasks. Those who merely evaluate computer performance generally do so as a contest with the physician, something never intended by the developers of any program.

Mount Sinai–IBM–Cro-Med Bionics Program and System

There have been many instances of aid by IBM to the developers of electrocardiographic computer programs. That aid has significantly involved the Mayo program and one developed at Mount Sinai Medical Center in New York City. IBM has now withdrawn from these efforts to concentrate on its own program. The Mayo Clinic is continuing its own efforts and another commercial concern, Cro-Med Bionics, has taken over the IBM development started at Mount Sinai.

Enderle[71,72] in Belgium has used this program clinically and has evaluated its 12 standard lead analysis output. In his study, four cardiologists evaluated the program results after agreeing on the criteria. Errors in measurement were the most frequent. These were generally attributable to artifacts and high amplitude complexes that caused signals to be missed on the early multichannel tape system used. They found few errors due to the logic itself. As noted for other programs, the errors found in these evaluations served as a basis for improvements.

Evaluation was made of 14,468 electrocardiograms from 9,968 patients. The records were normal in 18 percent. There was 87 percent overall agreement between computer and cardiologist. There was a 2.9 percent rate of disagreement on QRS rhythm and an 8.0 percent rate of disagreement on wave form contour. Contour errors were found in 693 tracings; these included T wave (2.6 percent) and QRS (2.8 percent) measurements.

In the newer version of this program a comparison program is used to identify significant changes in the electrocardiogram. It has been found that the electrocardiogram varies greatly from day to day and the di-

agnosis may change when the variation causes electrocardiographic values to exceed criteria cutoff points. Pordy and his group,[73–76] who have provided the major direction for this program, believe that physician overview is always required and is of paramount importance. They also consider that for complete clinical acceptance, it is required that the computer perform all the functions of the electrocardiographer and that the tracings should be stored to permit later retrieval for comparison of serial records and should also be readily obtainable on demand.

This program has often been used in conjunction with computer-interpreted three lead orthogonal electrocardiograms. Pordy has compared the standard 12 lead analysis made by his program with computer vectorcardiographic (Frank lead) systems. His data showed that the vector analysis "failed to disclose the clinical diagnosis evident in the 12 lead electrocardiogram."

Like the MSDL effort, this project started in the mid-1960's and has been considered a system; however, limited but usable rhythm analysis subroutines and comparisons were introduced earlier than in other programs. In this program, three arrhythmias are defined by wave form contours: pacemaker, first degree atrioventricular block and Wolff-Parkinson-White patterns. Other arrhythmias are interpreted with use of special subroutines that employ a "voting"-like procedure to determine which is present. The arrhythmias interpreted are those most commonly found in clinical practice. Pordy's studies at Mount Sinai suggest that the program has an 80 to 85 percent rate of accuracy in interpreting arrhythmias.

IBM Program

This program was initially developed using a sample test group of 400 electrocardiograms. Bonner (who was also a major contributor to the early Mount Sinai program) and the other developers of the IBM program[77] have evaluated their results in 1,435 records of which 1,008 were abnormal. They found that the computer had a 97 percent rate of correct classification in reference to gross categories of normality and abnormality and that 94 percent of all its statements concerning contour abnormality were correct; in the remaining 6 percent the statements were missing. In 1.2 percent of cases abnormal tracings were called normal. Ninety-three percent of normal electrocardiograms were correctly analyzed; errors were due to S-T and T wave changes. Overall, they reported 82 percent "completely acceptable" computer interpretations.

Referring to arrhythmias, there were 117 records with rhythm abnormalities and 7 with fixed-rate pacemakers. In 2.7 percent of 1,311 records with sinus mechanism the computer could not determine the rhythm. Of the 117 records with arrhythmias, 35 (30 percent) were also called undetermined and 9 of the remaining 82 interpretations were incorrect; the remaining 73 (62 percent) were correctly interpreted. There were 74 cases of atrial fibrillation or flutter-fibrillation; 77 percent of these were correctly diagnosed. There were 13 cases of second and third degree A-V block; only 3 were correctly analyzed. There were 63 cases with two or more ventricular premature beats; the data do not indicate results if only one such beat occurred. In the instance of two or more, there were either misses or calls of undetermined rhythm in 23 cases with a resulting 64 percent rate of accuracy. In instances when there were two or more supraventricular beats (no mention is made when only one occurred) there was 61 percent rate of accuracy. There are approximately 30 possible arrhythmia statements in their program, but not all appear to have been in the test or trial data used. With reference to arrhythmias, the data appear to be similar to those claimed by others in their programs but it is easier to abstract the data from the paper of Bonner et al. than from the others.

Bonner et al.[77] noted problems with diagnosis of left ventricular hypertrophy and modified their criteria; they report incorrect diagnoses of left ventricular hypertrophy in less than 1 percent of cases compared with a 7.2 percent rate by physician reading. This again appears to substantiate the impression, previously noted, that a physician does not follow any textbook criteria for hypertrophy as closely as a computer.

In 8 percent of 150 subjects, anterior infarction was unstated by the logic used. This was attributed to measurement error and logic inadequacy with regard to R wave progression in the precordial leads. In inferior myocardial infarction errors existed primarily attributed to measurements in ascertaining the presence of an initial R wave in leads II, III or aVF or the actual measurement of the Q wave depth and duration. The authors of this as well as those of other programs have implemented program refinements intended to compensate for some of this type of measurement and logic error.

On the basis of the authors' original criteria, ischemia was missed in 8 percent of cases. This was mostly due to the degree of T wave negativity required in the logic program. S-T depression abnormality was incorrectly read in 1.4 percent of the cases. The reason was primarily related to J junction changes in normal electrocardiograms. Unstated S-T abnormalities were almost all related to subtle delayed and sloping S-T segments caused by digitalis effect. To reduce this error the measurement program has been modified to measure S-T changes 90 msec after the end of the QRS complex. This may or may not always correspond to physician judgment but has also been done in other programs. Significant S-T segment elevations went unnoticed in 10 percent of S-T elevation abnormalities. This was a result of slight changes associated with inferior myocardial infarction and pericarditis, and the need for a program logic that would omit nonspecific S-T changes or early repolarization in normal electrocardiograms. In pulmonary disease, it was found that because of frontal plane angle and low voltage criteria, 7.6 percent of cases were missed.

The developers of this program and others have encountered difficulty in rhythm analysis in differentiating P and T waves in close or changing sequences. Transmission noise and interrupted identification sig-

nals were sometimes found to produce hign frequency spikes that, when interspersed between QRS complexes, produced supplementary statements, interpreting them as atrial or ventricular premature beats. This is common to other programs as well. The IBM program was analyzed and contrasted with two other programs, although by somewhat inadequate techniques, in the preceding discussion of the MSDL program.

Present status: The IBM program has been used to clinical advantage by its developers. The program uses multiple complexes from a lead to arrive at measurements. This procedure differentiates it from other programs and gives it the potential for precision although because it requires averaging and a larger data base it has some drawbacks and sometimes added costs. Crevasse and Ariet[78–80] have described the start of a regional computerized electrocardiographic processing center that uses this program. Although the center now links substantially more hospitals, it originally involved a central electrocardiographic processing facility at the University of Florida College of Medicine linking two distant and three local hospitals and five screening clinics. The "all-inclusive" cost for computer, telephone and data acquisition hardware was originally estimated to be $7.75 per electrocardiogram with an annual volume of 30,000 tracings.

Other Program Developments

Dreifus program: Scheinok et al.[81] reported on the development of a computer-aided electrocardiographic system of analysis that was used to process 85 percent of all inpatient tracings in a large urban hospital specializing in cardiovascular diseases. The system used physician over-read. A computer interactive method for physician editing, using visual display terminals, was planned. This program appears to combine aspects of various programs and its developers claim that criteria can easily be rewritten for it as the need arises. The program system produces on-line analog to digital and digital to analog conversion to photograph the graphic tracing. A microfilm copy is then placed on a punch card and a report applied to the punch card that can be viewed on a conventional microfilm viewer.

Talbot et al.[82] examined the criteria used for the diagnosis of myocardial infarction by this program which used 12 standard and 3 orthogonal leads. Clinical and cardiac catheterization data were used for definitive diagnosis. As might be expected, better results were obtained with orthogonal and 12 leads together than with either system alone for the diagnosis of myocardial infarction as well as infarction in association with left ventricular hypertrophy and conduction defects. The most sensitive criteria for anterior infarction were the Q/R wave amplitude relation in the 12 leads and loss of the first 20 msec of anterior forces in the horizontal and sagittal planes. However, false positive results were more frequent with the combined system than with 12 leads alone, particularly in association with left ventricular hypertrophy, nonspecific intraventricular conduction defects and left bundle branch blocks. V lead criteria were more specific. No single test with an acceptable false positive rate was sensitive for inferior wall infarction in all situations. These facts bear emphasis. Errors were sometimes caused by erroneous computer measurements but were more often due to inadequacies of criteria.

The opinions of Dreifus in reference to arrhythmias, quoted subsequently in this review, are based on his experiences with this program. He is mainly responsible for the program's medical formulation and guidance. Use of the program has generally been limited to the developer's site.

MacFarlane program[83–88]: MacFarlane et al. in the United Kingdom have designed a computer program for analysis of 3 lead and 12 lead electrocardiograms. This program, like the Dreifus effort, is primarily used at the developers' site. From a comparative study of computer-interpreted electrocardiograms, they have concluded that the 3 lead system used was clinically as acceptable as the 12 lead system with respect to computer-assisted analysis. The 3 lead system appeared to demonstrate greater correlation with clinical findings and was associated with fewer false positive interpretations than the 12 lead system used. In recent experiences with the earliest version of arrhythmia analysis the rhythm was interpreted correctly in 95 percent of cases.

In the 1st year of operation 7,703 electrocardiograms were recorded. Many modifications of criteria and wave recognition methods were incorporated into a second version of the program released early in 1972. The group's reports found two main sources of error, technical difficulties and programming. The technical errors were caused by faulty magnetic tape, inexperience of the technicians and incorrect electrode placement. In spite of every attempt to circumvent errors in programming logic, the authors, like others, have found that some electrocardiograms do not fit a well defined normal or abnormal pattern. This may be expected to continue to be the case for many years.

Arvedson program: It has been difficult to evaluate properly (because of lack of availability of his program) the work of Arvedson[89] in Sweden, but he too had an early three lead program.

Van Bemmel program: Van Bemmel et al.[90,91] in the Netherlands have had under development an automated vectorcardiographic/electrocardiographic system. They have used extensive wave form typing to improve quality of information before a detailed contour analysis. They described an interactive method for the automatic recognition of different types of QRS complexes. Consecutive QRS complexes are allocated automatically or by human interaction to clusters. Their efforts appear to be most promising. The simplicity and good documentation offered in many of the subroutines could greatly aid the development of other programs.

Arrhythmias

Development of arrhythmia analysis: It is reasonable from an economic viewpoint to try to program for the most common arrhythmias in a particular environment. The cost-effective problem has been to de-

TABLE II

Results of Computer Classification of Arrhythmias*

Arrhythmia	Total		Computer Classification
Atrial fibrillation	39	9	Correct
		9	Incorrect
		21	Missed
Ventricular premature beats	41	20	Correct
		12	Incorrect
		9	Missed
Atrial premature beats	33	0	Correct
		17	Incorrect
		16	Missed

*Data from Dreifus.[93]

termine how important it is to recognize each arrhythmia and what additional expense is valid if few data are usually available. The approach can produce few arrhythmia statements as in the earlier MSDL programs or more abundant and complex terminology as in the Mount Sinai, IBM and recent Mayo version.

Arrhythmias in a single lead are more difficult to analyze than those in multiple simultaneous lead systems, especially during exercise or monitoring. With simultaneity what may not be seen in one lead may be present in another so there is less likelihood of a false negative diagnosis.

Many complex mechanical and operational problems are caused by differences in duration of arrhythmias and their varying rates. A few arrhythmias require a small time interval for detection. Some need extremely long recordings and hence are uneconomic for today's clinical computer systems. Ventricular rhythms are generally easier to define than atrial rhythms.

Multiple P waves and asynchrony of P waves and QRS complexes pose severe problems. The T-P interval needs close attention to identify P waves, and this increases the cost of processing. Analog preprocessors and systems may be an effective mechanism for such processing in the future. Subroutines could also be developed for random sampling followed by more detailed subroutines when necessary. Storage of data for comparison may aid in rhythm analysis. Because criteria do not exist for total separation of waves in arrhythmias (for example, P versus T versus U), probability techniques may have to be used.

Artifacts, baseline shifts and muscle tremor are troublesome in this type of analysis. Minor changes in wave contour or respiratory-related amplitude changes in peak to peak QRS values are more subtle forms of difficulty.

After identification of an arrhythmia, measurement and analysis are needed to complete the process. Together the lack of agreement on diagnostic criteria and the diversity of arrhythmias cause the most significant programming problems. A review of texts on arrhythmias shows that 700 different rhythm statements can be made; thus it is not yet practical to program for the large variety of overlapping diagnoses possible, considering, in addition, that arrhythmias do not always follow dogmatic rules and are generally variable.

The general conclusion that can be made regarding computer electrocardiographic arrhythmia programs is that most programs are still in a state of early development.[92] It is yet too early to judge or make valid program comparisons in this field because of rapid improvements.

The Dreifus arrhythmia program: Dreifus[93] examined 1,105 hospital electrocardiograms processed by computer. Ten percent had arrhythmias. His findings (Table II) appear to be representative of many programs.

Dreifus has listed some problems of rhythm analysis by computer:

1. Some records cannot be sufficiently well recorded for computers because the patient is too ill to allow artifact-free tracings.
2. Atrial fibrillation with a wide QRS complex makes it difficult to find ventricular premature beats.
3. Enough sample and computer time to analyze the rhythm is a serious cost (or computer size) problem.
4. Signal noise in the baseline obscures P waves and there may not be enough time in a real-time analysis to examine the tracing in detail unless extremely powerful computers are used.
5. Some records can never be interpreted by the computer. They require special techniques of electrocardiographic recording.
6. Some arrhythmias are too rare and complex. Attempts to make logic for these rhythms may be inappropriate.

Dreifus adds that:

1. The differential diagnosis of supraventricular from ventricular mechanisms should be done but all the rules are not yet established.
2. Since P wave recognition is difficult, one should try to program around them and do without it if possible.
3. Artifacts may always pose problems and sometimes cannot be differentiated from arrhythmias.
4. Coexisting arrhythmia mechanisms will be difficult to analyze.
5. Inadequacy of human logic in defining the arrhythmia is a primary problem.

Dreifus suggests that we need better arrhythmia programs but that they need not be very sophisticated. We need only identify six or so rhythms for useful purposes. He suggests the following: A-V block (first, second and third degree), ventricular premature beats, atrial premature beats, atrial fibrillation, atrial flutter and pacemaker rhythm.

The Willems, Pipberger program: These general suggestions can be contrasted with the results of Willems and Pipberger.[94] They have developed a digital computer program for automatic interpretation of what they consider the most common arrhythmias that do not require extremely long time intervals. Their program was developed using a training set of 543 "short" (6 second) and 179 "long" (10 second) records obtained in 344 patients with various arrhythmias. The logic was tested on an independent file of 450 short and 207 long records subsequently obtained from another 239 patients. In addition to these arrhythmia records, the authors analyzed 545 short and 176 long records con-

sisting mainly of normal sinus rhythm or of sinus arrhythmia. These tracings were recorded in a study of the day to day variability of the orthogonal electrocardiogram and vectorcardiogram. Half of these records were used in the study file and the remainder in the independent file, thereby giving a combined total of 1,538 "short" and 562 "long" records. A cardiologist with no prior knowledge of the computer analysis made a rhythm diagnosis of the independent records. Tracings with sinus rhythm (the dominant rhythm diagnosis) were classified into three groups:

Group 1. Cases with noncomplicated normal sinus rhythm; cases with sinus bradycardia and those with short P intervals were treated separately.

Group 2. Cases with dominant rhythm of sinus origin, complicated by the presence of premature ventricular contractions with bigeminy or trigeminy or atrial premature contractions but without A-V block.

Group 3. Cases with sinus rhythm complicated by first degree A-V block, with or without associated premature ventricular or atrial beats or bigeminy.

Willems and Pipberger found the recognition rate of sinus rhythm in Groups 1 and 2 to be between 86 and 97 percent. The remaining cases in these groups were most often evaluated as showing regular rhythm without further specification as to the origin of the rhythm. This occurred mainly in noisy records. In a few cases, the diagnosis of A-V junctional rhythm was made with flat P waves in lead Y. These cases also caused decision problems for the cardiologist in his attempt to determine the rhythm origin. The computer recognition rate of sinus rhythm in cases with a prolonged P-R interval (Group 3) ranged from 64 to 80 percent. This lower rate was attributed mainly to problems of recognition of P waves occurring close to the preceding T wave. In 20 percent of the cases with A-V block the P-R interval was greater than 250 msec, and almost all the failures occurred in this group.

In the short learning and short independent records, Willems and Pipberger found that atrial fibrillation was correctly determined in 86 and 80 percent of cases, respectively. The sensitivity for atrial fibrillation detection was 10 percent higher when long records were analyzed. For all cases with atrial fibrillation combined, the correct diagnosis was obtained in 82 percent (179 of 217) of 6 second records and 92 percent (83 of 90) of 10 second strip recordings. When the program failed to reach a conclusive diagnosis of atrial fibrillation, the statement "arrhythmia" was printed without further specification in 10 and 4.5 percent, respectively, of short and long records. In 4 of 217 short (6 second) records and in 1 of 90 cases with long (10 second) records of atrial fibrillation, the diagnosis of sinus arrhythmia or sinus rhythm was erroneously made.

In the tabulation of aberrant beats, no distinction was made between ventricular premature beats and atrial premature beats with aberrant conduction. The recognition rate ranged between 83 and 91 percent in the various subgroups of long and short records from the study and independent files. Among the short records, 259 of 299 aberrant beats (86 percent) were correctly recognized, with 14 false positives in a total of about 10,000 normal beats. For the long records, 181 of 206 abberant beats (88 percent) were recognized, with 16 false positives in a total of about 6,180 normal beats. The incidence rate of false positives was 1.4 and 2.6 percent for short and long records, respectively. Of the false positives, four were in cases with atrial fibrillation, in which QRS complexes vary slightly in configuration from beat to beat. The remaining false positives were mainly due to spikes or tape noise in the P-T segment or superimposed on QRS complexes.

In the computer diagnosis of less common rhythm abnormalities, Willems and Pipberger found that of the 67 cases with short records and sinus arrhythmia as judged by simple eye reading, 39 were identified correctly. In 8 the statement "arrhythmia" was printed, whereas in 17 others, normal sinus rhythm or sinus bradycardia was printed. As could be expected, the detection of sinus arrhythmia was better in cases with long records. The results were the same for detection of atrial premature beats, complete A-V block, bigeminy and trigeminy. Only one false positive diagnosis of atrial premature beats was made.

Present status of arrhythmia analysis: The data on rhythm analysis in computer programs are sparse. Capability figures range from 60 to 95 percent. However, such figures fluctuate depending on what one initially decides the criteria of judgment should be. Whether every clinic and practice needs a program that will classify all rhythms or only specific arrhythmias is an important cost consideration. Techniques have been described to suit specific purposes and interests. The variety of ideas and implemented programs suggests the changing nature of this field.[94–102] Feldman[103] has indicated that a decade of research on using computers to monitor the heart rhythm of patients with cardiac disease has resulted in the development of at least 20 different systems as well as the installation of approximately a dozen commercial systems for routine clinical use for intensive care and monitoring.

Arrhythmia diagnoses are primarily generally limited by deficits in logic. To adapt answers to users, several new commercial systems allow editing of computer answers by each user. As a result of continuing interaction, improvements in program developments can be expected.

Exercise Programs

There is considerable interest today in electrocardiographic monitoring for diagnostic exercise testing, for physical fitness studies at work evaluation centers and for management of acutely ill patients in coronary care units. These activities place a large burden on electrocardiographers. In response to their need, there has been rapid growth in the development of electrocardiographic telemetry equipment and monitoring systems. Some current monitoring systems are actually analog computers. These are generally limited to tracking heart rate and rhythm.

Problems in stress testing with computer electrocardiography: Full analysis of an electrocardiogram

from an active subject requires a different approach from that used in the resting state because of the greater frequency of distortions that complicate recognition of patterns. During activity, the electrocardiographic record may include shifting baseline, noise artifact, superposition of wave forms, changing heart rate over a wide range, abnormal conduction and arrhythmias. The finding that gives the exercise electrocardiogram its greatest clinical value is ischemia-induced wave form alteration that must be detected and distinguished from the other named events.

Many researchers have assessed the uses and limitations of stress testing in the evaluation of ischemic heart disease. One of the most critical problems is obtaining an optimal electrocardiographic signal from which to compute the S-T segment changes. Unfortunately, noise artifact produced by exercise causes considerable interpretive difficulty when the exercise electrocardiogram is manually processed. Consequently, increasing attention has been focused on digital computer techniques to attempt to eliminate subjective error in measurement by reduction of signal artifacts.[104] These methods most often rely on the fact that a large percentage of noise in a typical exercise record occurs at random and can thus be eliminated by averaging methods. However, any averaging process as it cleans the signal may eliminate transient changes that may be useful in diagnosis. Alternating current noise can be eliminated by 60 hertz notched filters or low-pass filters (30 to 40 hertz), although electrocardiographic signal distortion may occur with cutoff frequencies as low as 30 hertz. Signals can also be eliminated by these techniques.

Baseline shift also presents undesirable problems. Attempts have been made to reduce or eliminate it by low frequency filtering in the range of 1 to 2 hertz. However, Berson and Pipberger[105] have demonstrated that absence of usual low frequency components produces distortion of the electrocardiographic signal. No standard value is yet universally used so that diagnostic (and computer) criteria must hence fluctuate with the initial signal acquisition device characteristics. Until some standardized value is decided upon for producing signals that are identical (in spite of some distortion) from one machine to another, criteria for analysis used by either physician or computer cannot be entirely adequate.

Rosner and Jackson and their co-workers[106,107] described one of the earliest digital computer systems for exercise electrocardiograms. The basic steps of that effort illustrate the general need. The QRS complexes in a specified time frame of data were identified by minimal derivatives, and the R-R interval between consecutive beats was measured to detect a cardiac irregularity. The values of the measurement of the first analyzed cardiac cycle were retained as a template. Measurements from succeeding time frame analyses were compared with this template. If all measurements were within the variation permitted by the criteria, the statement "No Significant Change" was printed in place of the measurement values for that time interval. If one or more of the measurements exceeded the criteria, the values of the "changed" beat were printed, and these new values replaced the previous template for comparison with subsequent measurements.

There are several difficulties in criteria generation that affect the results. Other physiologic variables such as respiration have an effect and have been considered. Elliott et al.,[108] for example, have described a computer technique for simultaneous recording and analysis of electrocardiographic and respiratory responses to graded exercise.

A computer technique permitting the continuous recording of selected points of electrocardiographic wave form during and after graded exercise in young untrained subjects has been described by Davies et al.[109] It is in adjustment of values to graded exercise that the computer may play its most useful clinical role. The wide scatter of values they observed, including some exceeding previously accepted values of normality, suggests the need for better criteria. Several computer programs are now being designed for on-line monitoring of electrocardiographic variables related to the S-T segment and T wave and other factors during exercise testing. The potential clinical importance of new efforts may improve knowledge regarding delineation of time-dependent changes in electrocardiographic wave forms during graded stress.

Regardless of much ongoing work, we lack programs that function as might be desired *during* exercise. It may be parenthetically stated that for the usual clinical purposes, results of computer analysis are generally good with any standard electrocardiographic program if the patient is asked to pause for a few seconds while a 12 lead record is made. This is not difficult on any automatic three channel 12 lead (or vector) electrocardiograph.

Computer analysis of rest and exercise electrocardiograms has been extensively investigated by Rautaharju and Wolf and co-workers.[114–116] In this Canadian research, there has been extensive work in review of programs and noise levels. They have indicated that if the root mean square value of noise is less than 60 μv, then in 95 percent of measurements precision is $\pm$10 msec for QRS, $\pm$20 msec for other intervals and $\pm$25 μv for amplitudes. These values of course depend on unique equipment and situations, and may warrant modification in the hands of others. In these efforts clusters of beats are used to identify homogeneous QRS complexes, for example. The D. C. Veterans Administration measurement program is used by these researchers for clinical interpretation. During exercise, a vector of the S-T segment is used. The lead with the most ischemic (and most elevated) S-T segment is selected from all leads and those measurements are used. In this way, measurements with a greater probability of error are excluded. Normal values have been generated from test studies. With rigid techniques used to record and test for noise, there was a 2.6 percent rate of error in QRS-ST measurement and a 1.3 percent rate of exces-

sive noise. Several thousand exercise records have been reviewed visually to evaluate the system, and they have found the results satisfactory.

Comparison Programs

There has been increasing emphasis on comparison programs. Comparison of several records is more limited by hardware needs (tapes, discs and other equipment) and by economics than by the logic of comparison. Comparison is a method for electrocardiographic data compression and serial analysis. The comparison routines in computer use today concentrate principally on the diagnosis of myocardial infarction and are not yet at high levels of technologic sophistication. In effect, the comparison problem is a first order limitation.

The problem of comparison of electrocardiograms is best discussed when there has been a firm decision regarding the hardware intended for utilization and after an institution's specific needs and present equipment have been considered. For computer comparison to be useful, one must plan to computerize all electrocardiograms taken. The anticipated volume will determine whether to depend upon an inhouse or an outside service bureau for economic operation. The comparison operation must, of course, fulfill a variety of needs of outpatient clinics and inpatient service facilities. A system that does not have the intrinsic capability of comparison at the time the electrocardiogram is taken is not within the overall *future* needs of the majority of medical institutions. The initial needs that an on-line comparison system can fulfill are those that would allow comparison operations to provide instruction to technicians when the transmitted data present problems or there is a change in the patient's status.

If on-line comparisons are not feasible, data can be processed off line, using punch cards as the interface with a central computing system. The central computer can then perform comparisons limited to diagnostic changes.

Comparison components: The program's requirements are:

1. *Data for comparison:* The electrocardiographic computer's output should contain: (a) necessary patient identification, (b) date of the tracing, (c) time of day of the tracing, and (d) the codes and required data for each of the various electrocardiographic interpretations and any comparisons previously made.
2. *Possibilities for correction:* The programs for comparison systems should allow the system to be used as a corrective subsystem. A physician should be able not only to add interpretations but also to delete items and otherwise alter the output to suit specific needs. For each patient, the system should house each interpretation as it is made by the electrocardiographic computer. Whenever corrections and new interpretations are added with use of punch cards (or other alternates), new interpretations should be made.
3. *Noncomputer interpretations:* The system should also allow noncomputer interpretations to be incorporated easily and compared.

Existing comparison programs: Pryor et al.[117] have reported an evaluation of a method of serial analysis by computer. They recognized the importance of computer-performed comparative analysis of electrocardiograms taken at different time intervals and found that little time was saved if the cardiologist having access to computer interpretations was required to make serial comparisons with previous tracings on the patient. Pryor's group[118] has also developed a program to compare tracings now included as a part of their automated interpretation routine.

The comparative program is operative only in the case of patients who have two or more electrocardiograms taken during a particular admission to the hospital. Thus, with this restriction on the data base, the program is used primarily to follow the serial changes of patients with acute myocardial infarction in the coronary care unit. Additional work is continuing to add diagnostic statements to confirm a tentative diagnosis indicated by the rhythm or wave contour programs. Pryor et al. call attention to problems of comparison in using computer-generated statements or values, or both. Errors can result from slight changes in value, such as QRS amplitude near levels at which criteria cutoffs exist. The question is whether changes of clinical significance exist even though values have changed, apparently significantly. Signal noise compounds the problem. Comparison of electrocardiograms has also been developed by the Pordy and MacFarlane programs.

Basic to any comparison is the need to consider coding of electrocardiograms when initially taken. Booth and Hull[119] produced an early coding system used by the MSDL program and now available for the IBM version. The "Minnesota code" has been popularized through its use in the World Health Organization.[120] It is suitable for epidemiologic studies but is not popular in clinical work because it does not correlate diagnosis with wave configuration; however, the code does lend itself to computerization. A new carefully documented coding system to be used in computers has been recently designed by Robles de Medina[121] in the Netherlands.

Pacemaker Analysis Systems

Tens of thousands of persons in the United States today depend on permanent cardiac pacemakers, and the number is increasing yearly. The failure rate of pacemakers is sometimes estimated to be 50 percent after 20 months of use. Thus, frequent observation of the pacemaker's functions and the corresponding electrocardiograms produced allow one to anticipate failures. Eighty percent of pacemaker failures now are caused by battery exhaustion although newer batteries, including the nuclear-powered variety, may change this outlook. Pulse generators generally have a rate change feature as a function of decline in battery voltage (that is, each triggered unit has a magnetic switch driving the unit to an asynchronous rate related to the battery voltage). As a result, heart rate data transmitted over the telephone lines by means of a frequency-modulated carrier can detect a reduction in battery power.

Several pacemaker analysis systems have been developed that permit evaluation of pacemaker function in the patient's clinic or physician's office or even his home.[122] In such systems, an electrocardiographic transmitter is used to send the patient's electrocardiogram or pacemaker artifact over standard telephone lines to a computer system for immediate analysis. One in-hospital system was developed at the George Washington University Medical Center as a result of previous experiences with MSDL-transmitted electrocardiograms.[123] Several groups perform similar analyses. The computer electrocardiographic programs designed for diagnostic purposes should be, but generally are not, capable of analyzing pacemaker malfunction. The majority of programs recognize pacemaker rhythms to a varying extent.

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Prolapse of the Mitral Valve (Floppy Valve) Associated With Ebstein's Anomaly of the Tricuspid Valve

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Prolapse of the mitral valve is described in two patients with the Ebstein's anomaly of the tricuspid valve. This association has not been described previously. It is probable, however, that this association is not a rare one, but that clinical features of the prolapsing mitral valve are obscured by those resulting from the malformed tricuspid valve. Opportunity also was provided to study anatomically the mitral valve of a patient known to have a systolic click and a late systolic murmur (the Barlow syndrome). Although there have been several anatomic descriptions of floppy mitral valve at necropsy, they have been extremely rare in patients known to have the classic auscultatory features of the Barlow syndrome.

Ebstein's anomaly of the tricuspid valve is usually either isolated or associated with a fossa ovalis type of atrial septal defect. The Ebstein type of anomaly is also extremely common on the left side of the heart in patients with corrected transposition of the great vessels. Pulmonary stenosis, ventricular septal defect, hypoplastic pulmonary trunk, hypoplastic ascending aorta and pulmonary atresia with intact ventricular septum are other cardiac malformations that occasionally occur in patients with Ebstein's anomaly. This report describes two patients with Ebstein's anomaly who also had prolapsing posterior mitral leaflets, an association that, to our knowledge, has not been described previously.

Report of Patients

Case 1

An 18 year old girl was found to have a precordial murmur at age 4 years. Although she led an active life she never had symptoms of cardiac dysfunction. Fourteen months before death she had a fracture of the right femur and was found to have Ewing's sarcoma. Her condition progressively deteriorated thereafter and she had widespread metastases. During the last 14 months she was admitted on several occasions to the National Cancer Institute. The blood pressure was 100/60 mm Hg. The neck veins were flat. The heart was large (Fig. 1), and a prominent impulse was palpated along the left sternal border. The heart sounds were normal and the second heart sound, heard at the base, was split normally. A systolic click was heard over the cardiac apex. A grade 3/6 late systolic murmur of the regurgitant type was heard over the precordium, left axilla and left side of the back, and it was loudest over the apex. No diastolic murmur was audible. The electrocardiogram (Fig. 2) revealed sinus tachycardia, nonspecific ST-T wave changes and an intraventricular conduction defect (QRS interval 0.09 second).

At necropsy, she weighed 41 kg, and the bone tumor had metastasized widely. The heart weighed 300 g and the posterior wall of the right ventricle was thin and bulged prominently posteriorly (Fig. 3). The right atrium was huge. The entire septal and posterior tricuspid valve leaflets were displaced downward to the point where their basal attachment actually was to the endocardium of the ventricular septum (Fig. 3). Most of the anterior tricuspid leaflet arose normally from the true tricuspid valve anulus. The most caudal portion of the displaced tricuspid valve formed an accessory orifice about 2 by 2 cm. The outflow portion of the wall of the right ventricle was of normal thickness.

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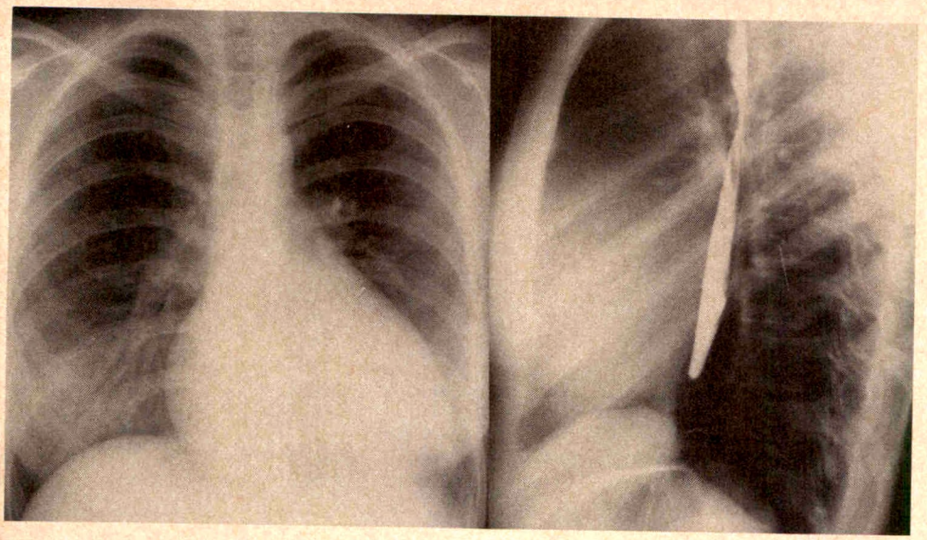

FIGURE 1. Case 1. Chest roentgenograms demonstrating mild cardiomegaly with right ventricular prominence, normal pulmonary vascularity and normal-sized left atrium.

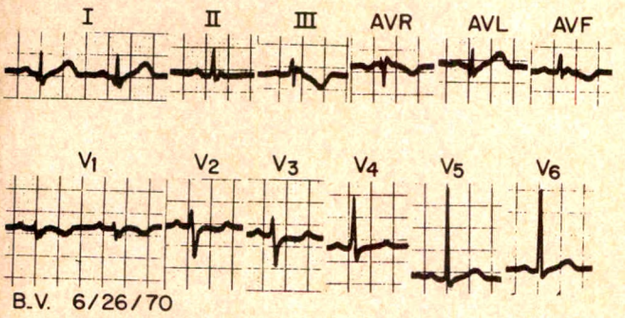

FIGURE 2. Case 1. Electrocardiogram.

The left atrium was of normal size. A valve-competent patent foramen ovale was present (Fig. 3). The mitral leaflets were focally but extensively thickened and the posterior leaflet protruded abnormally backward toward the left atrium during simulated ventricular systole (Fig. 4). The left ventricular cavity appeared mildly dilated. Both semilunar valves were normal. Histologic study disclosed a marked increase in the amount of acid mucopolysaccharide material in the mitral valve leaflets (Fig. 4).

Case 2

A 35 year old woman was found to have a precordial murmur when pregnant at age 21 years. After a full-term normal pregnancy and normal delivery she was admitted for evaluation of the murmur. She had always been entirely asymptomatic despite participation in strenuous activities. A brother had died of a cardiac condition at age 5 months, and a niece had had a cardiac operation for a congenital cardiac defect. On examination, an impulse and systolic thrill were palpated along the left sternal border. The second heart sound was widely split and the interval between its two components did not vary with respiration. A grade 2/6 systolic murmur was audible along the left sternal border. The chest roentgenogram (Fig. 5) disclosed pectus excavatum and slight cardiomegaly. The electrocardiogram revealed sinus rhythm and incomplete right bundle branch block (QRS interval 0.10 second). At cardiac catheterization (Table I), Cardiogreen® dye curves

TABLE I

Case 2: Intravascular Pressures (in mm Hg) at Cardiac Catheterization

	Age (yr)		
	21*	23	33
Pulmonary artery	18/4	15/5	24/14
Right ventricle	18/2	15/3	24/9
Right atrium			
Mean	1	2	8
v wave	. . .	5	10
Pulmonary arterial wedge	. . .	. . .	14
Systemic artery	90/55	110/54	90/60
Left ventricle	. . .	. . .	90/13

*Preoperative data before closure of atrial septal defect at this age.

revealed a left to right shunt at the atrial level. The arterial oxygen saturation was 98 percent. At operation, the right atrium was very dilated and the tricuspid valve was displaced caudally. A defect, approximately 3 by 3 cm, was present in the midportion of the atrial septum and was closed with a Teflon® patch. The immediate postoperative period was uneventful.

Postoperative course: When seen 20 months postoperatively (at age 23), she was asymptomatic and had given birth to another child without difficulty. Reexamination disclosed a left parasternal impulse and a grade 1/6 early systolic murmur along the left sternal border. The second heart sound was normal. The electrocardiogram and chest roentgenogram were unchanged. Cardiac catheterization revealed normal intracardiac pressures (Table I) and no shunts.

At age 31 (10 years postoperatively) the chest roentgenogram showed more cardiomegaly. She remained asymptomatic until age 33 when paroxysmal atrial tachycardia with varying block suddenly developed. Reexamination disclosed elevated mean central venous pressure, normal cardiac sounds, a systolic click, and a grade 3/6 pansystolic murmur loudest over the cardiac apex with radiation into the left axilla. The murmur did not increase during inspiration. The chest roentgenogram (Fig. 5) now showed massive enlargement of the right atrium. The electrocardiogram revealed atrial tachycardia and a right ventricular conduction defect.

Cardiac catheterization (Table I) revealed no shunts; the cardiac index was 1.7 liters/min per m^2. Right atrial and right ventricular cineangiograms disclosed marked enlargement of the right atrium and caudal displacement of the tricuspid valve (Fig. 6); the levophase showed enlargement of the left atrium. The left ventriculogram showed mitral valve prolapse (Fig. 6). The presence of ventricular premature beats during the latter procedure prevented definitive determination of the presence or absence of mitral regurgitation.

During the past 3 years she has received quinidine daily and has had no further arrhythmias. Echocardiographic studies have been obtained, and they are consistent with the diagnosis of mitral valve prolapse.

Comments

Mitral valve prolapse in Ebstein's anomaly: It is now well recognized that the mitral valve prolapse syndrome is a common condition, most often presenting as a mid-systolic click with or without a late systolic murmur. It occurs in all age groups, newborn to elderly, and it is probably more frequent in women. Although severe chest pain, serious ventricular arrhythmias and sudden death may occur, mitral valve prolapse is usually a benign condition. The "mid-systolic click and late systolic murmur syndrome" (the Barlow syndrome) probably occurs most frequently in persons without other evidence of cardiac disease, but mitral valve prolapse has been described in persons with underlying cardiac disease, including the Marfan syndrome, trauma, atrial septal defect, hypertrophic cardiomyopathy and even ischemic and rheumatic heart disease.[1-6] Its occurrence in patients with the Ebstein anomaly has not been described previously. The reasons may be several: (1) The association may be rare; (2) auscultatory findings, namely, the systolic click and mid-late systolic murmur, may be obscured by the murmur of tricuspid regurgitation and also by flow murmurs resulting from a right to left shunt at the atrial level, a left to right shunt at the ventricular level, or both; (3) left ventricular angiographic studies are infrequently performed in patients with Ebstein's anomaly; (4) there may be no

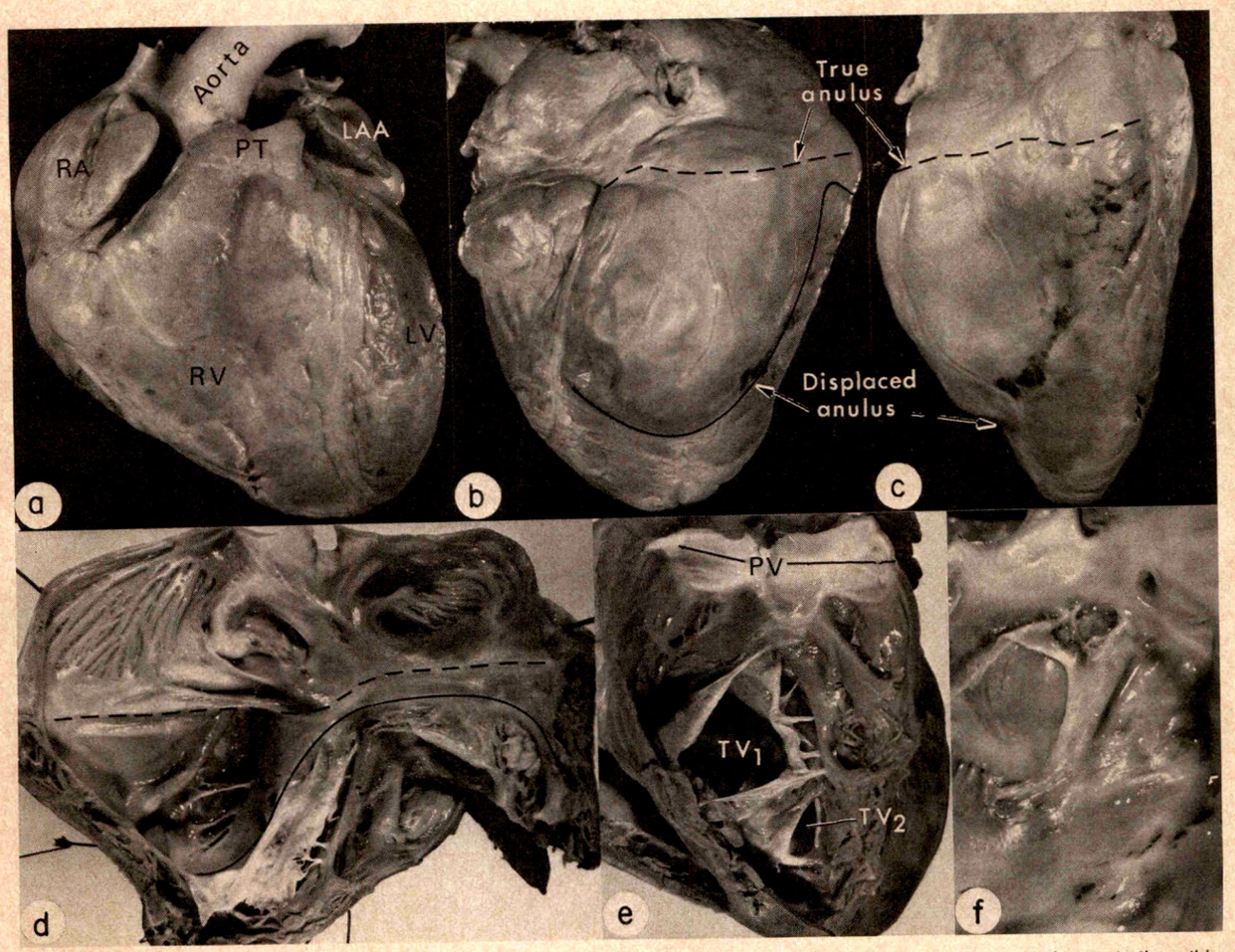

FIGURE 3. Case 1. The heart at autopsy. **a, b** and **c,** anterior, posterior and lateral views, respectively, of its external aspects demonstrating a thinned parchment-like (atrialized) right ventricular wall bulging posteriorly above the attachment of the tricuspid valve leaflets. **d,** opened right atrium (RA) and ventricle (RV) showing marked downward displacement of the posterior and septal tricuspid leaflets. The atrialized portion of the right ventricle behind the posterior leaflet is the part that bulges (**b** and **c**). **Dashed line** = true anulus; **solid line** = anulus in this patient. **e,** tricuspid valve (TV) from below displaced deep into the right ventricular cavity. Two valve orifices are present (TV_1 and TV_2). **f,** intact atrial septum from the left atrium with a valvular-competent foramen ovale. The patient was never cyanotic. LAA = left atrial appendage; LV = left ventricle; PT = pulmonary trunk; PV = pulmonary valve.

evidence of mitral regurgitation; (5) typical electrocardiographic features of mitral valve prolapse, namely, T wave and S-T segment changes suggestive of posterior wall ischemia, may be overshadowed or obscured by the changes produced by Ebstein's anomaly; and (6) because an association between Ebstein's anomaly and mitral valve prolapse has not been recognized previously, the clinical features of this syndrome have not been carefully sought for.

Mitral valve prolapse was suspected in Patient 1 after auscultation, and in Patient 2 diagnosis was made with angiography. The levophase of the right ventricular cineangiogram suggested prolapsing mitral valve, and this diagnosis was confirmed by left ventricular cineangiogram.

The major characteristic of Ebstein's anomaly is a caudal displacement of the basal attachment of the tricuspid valve so that it inserts onto the right ventric-

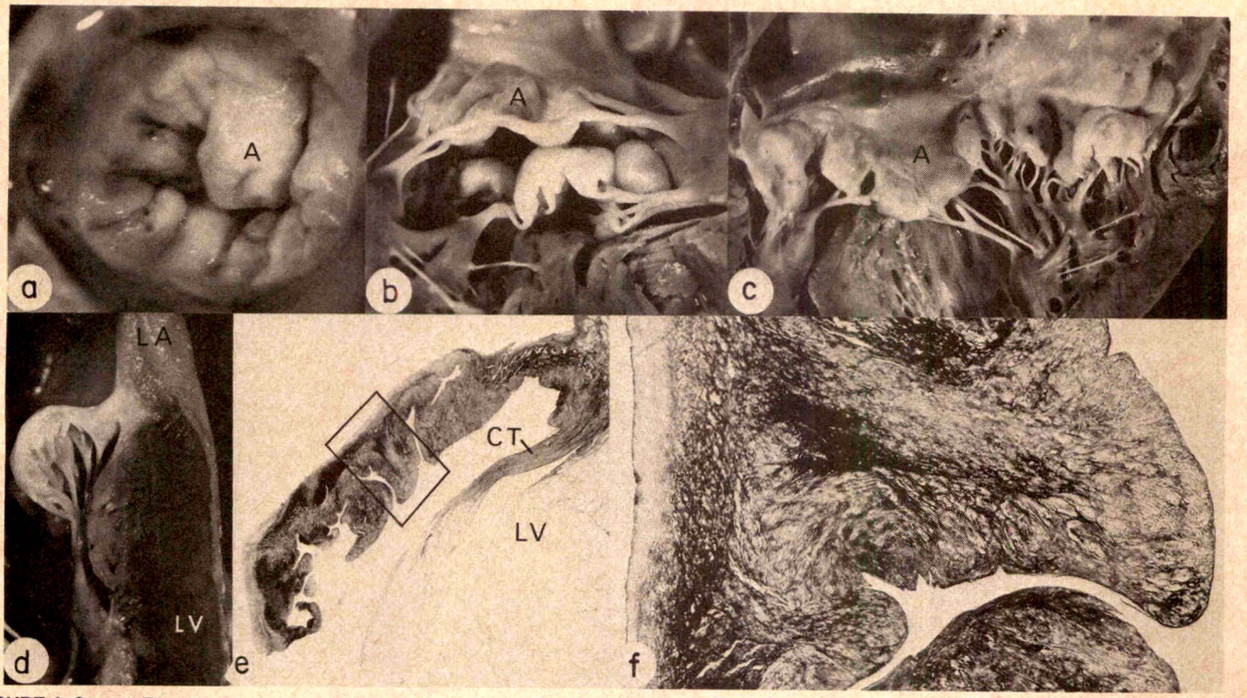

FIGURE 4. Case 1. The mitral valve. **a,** prolapsed mitral valve leaflets as viewed from the left atrium. **b,** view of floppy leaflets from the left ventricle. **c,** opened valve showing elongated and focally thickened anterior (A) and posterior leaflets. **d,** longitudinal section through the left atrium (LA), posterior mitral leaflet and left ventricle (LV) showing the billowed posterior leaflet. **e** and **f,** photomicrographs of a portion of the posterior leaflet demonstrating focal thickening and increased acid-mucopolysaccharide deposits (dark staining). CT = chordae tendineae. (Acid-mucopolysaccharide [Reinhart] stains [**e** and **f**]: × 5 [**e**] and 36 [**f**], reduced by 22 percent.)

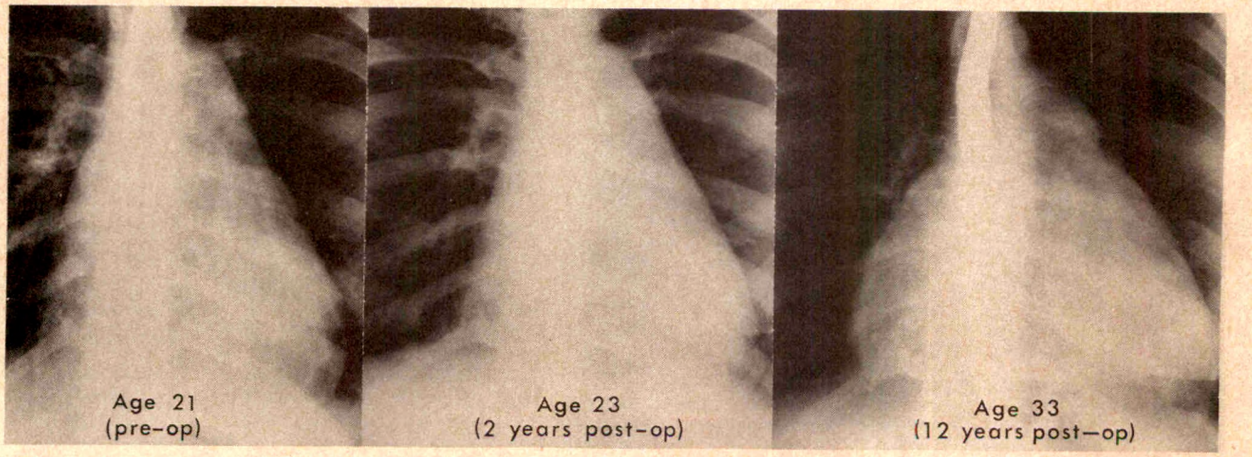

FIGURE 5. Case 2. Posteroanterior roentgenograms obtained on three occasions during a 12 year period. The left and center radiographs are similar, each showing mild cardiomegaly with prominent "main pulmonary segment," normal pulmonary vascularity and a normal-sized left atrium. The radiograph taken at age 33 (12 years after operation) shows a significant increase in cardiac size with enlargement of the right atrium.

ular free wall or, in some cases, onto the ventricular septum. The second major characteristic of Ebstein's anomaly is a striking redundancy of the tricuspid leaflets. The displacement of these leaflets into the right ventricle and their close adherence to the underlying mural endocardium account for the absence of atrial prolapsing of these leaflets during ventricular systole. Thus, if, as in Ebstein's anomaly, the right atrioventricular valve is redundant, that is, floppy, it might be anticipated that the chance of finding redundant or floppy mitral valve leaflets would be increased.

Patients with an atrial septal defect have an increased frequency of mitral valve prolapse.[7–12] Obviously, patients with Ebstein's anomaly often have defects in their atrial septum. This association may account in part for the association of mitral valve prolapse with Ebstein's anomaly. One of our patients had a valvular competent patent foramen ovale; the second had a large fossa ovalis defect that required operative closure.

Anatomic findings in mitral valve prolapse: Although there is much clinical information, there is a striking paucity of anatomic information on patients with the "mid-late systolic click late systolic murmur syndrome."[2] The reason, as mentioned earlier, is simply that this clinical syndrome is usually (but not always[13]) benign. Thus, Case 1 provides an opportunity to study

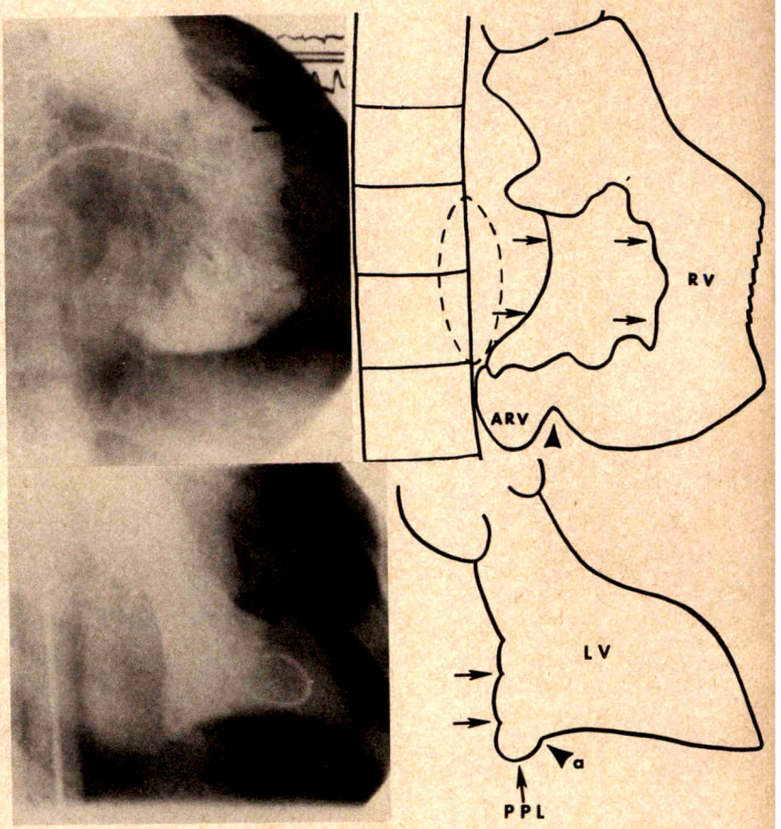

FIGURE 6. Case 2. Right ventriculogram with line tracing **(upper panels)** in the posteroanterior projection demonstrates during diastole leftward displacement of the tricuspid valve **(arrows). Dotted lines** indicate the normal position of the tricuspid valve. The inferior border of the right ventricle (RV) is notched at the demarcation between the "atrialized right ventricle" (ARV) and the body of the right ventricle. The left ventriculogram with line tracing **(lower panels)** in the right anterior oblique view during systole demonstrates prolapsing posterior leaflet (PPL) of the mitral valve over its anulus (a) into the left atrium. The posterior leaflet is scalloped **(horizontal arrows).** LV = left ventricle.

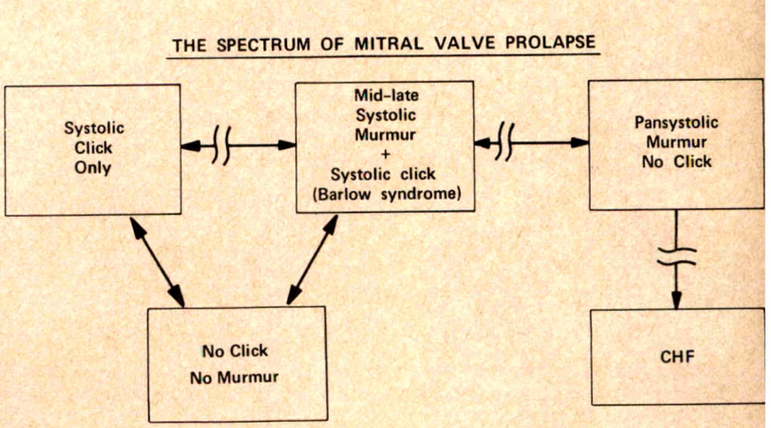

FIGURE 7. Diagram showing likely auscultatory progression in the prolapsing mitral valve syndrome (see text). CHF = congestive heart failure.

a floppy valve anatomically in a patient who had no symptoms of cardiac dysfunction as a result of the "floppiness." This patient died of a malignant neoplasm, not of cardiac disease. Both mitral valve leaflets were thickened and their area was increased in a transverse dimension. Interestingly, the dimensions of the leaflets from their basal attachments to their distal margins were not increased and, furthermore, the chordae tendineae were not elongated; indeed, many appeared shorter than normal. Thus, elongation of the chordae tendineae is not necessary for a mitral valve leaflet to prolapse toward the left atrium during ventricular systole.

Spectrum of mitral valve prolapse: In patients with severe mitral regurgitation due to prolapse of one or both leaflets, a systolic click is rarely present and the systolic murmur is pansystolic rather than occurring only in the late or mid-late phase of systole. It is likely, as has been suggested previously,[4,14] that some or all of these patients may have had lesser degrees of prolapse at an earlier time, and the process progressed as shown in Figure 7. A prolapsing but competent valve leads to an isolated click, a prolapsing valve that overshoots its coapting cusp only in the latter part of systole may result in the late systolic murmur with or without retention of the systolic click. As the prolapsing becomes even more severe, regurgitation occurs both in early and in late systole; the murmur thus becomes pansystolic and the click vanishes. Recent electrocardiographic studies[15,16] have demonstrated that the click or the late systolic murmur, or both, may disappear entirely during some cardiac cycles; the changes are associated with a change in appearance of the type of posterior leaflet prolapse, that is, late systolic prolapse alternating with holosystolic prolapse. Once regurgitation occurs throughout systole, however, and is relatively persistent, it is unlikely that reversion to one of the early stages will occur (Fig. 7).

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Congenitally Corrected Transposition of the Great Vessels: Localization of the Site of Complete Atrioventricular Block Using His Bundle Electrograms

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Complete atrioventricular block proximal to the bundle of His in a patient with congenitally corrected transposition of the great vessels was documented using His bundle electrograms. The spontaneous rhythm probably originated from the bundle of His and was responsive to carotid sinus massage, atropine and isometric and treadmill exercise. These electrophysiologic observations are consistent with recent anatomic studies of congenitally corrected transposition of the great vessels.

Disturbances in atrioventricular (A-V) conduction occur frequently in patients with congenitally corrected transposition of the great vessels and may be responsible for syncope and sudden death.[1–3] The electrophysiologic characteristics of these conduction disturbances have been studied by bundle of His recording in only three previously reported cases.[4,5] In two additional cases, direct recordings from the His-Purkinje system were obtained during surgical repair of an associated ventricular septal defect.[6] None of the five patients had complete A-V block. In this report we describe the successful localization of the site of complete A-V block using bundle of His recordings in a patient with corrected transposition of the great vessels.

Case Report

An asymptomatic, active 20 year old man was referred for evaluation of a heart murmur. The blood pressure was 110/80 mm Hg and the heart rate was regular at 72/min. Carotid and femoral arterial pulses were normal. The lungs were clear. The second heart sound was split physiologically, with the first component loudest in the second left intercostal space. An ejection click in the second left intercostal space initiated a grade 2/6 crescendo-decrescendo systolic murmur. The click did not vary with respiration.

The electrocardiogram (Fig. 1) revealed complete A-V block and the tracing as well as the chest roentgenogram suggested the diagnosis of congenitally corrected transposition of the great vessels. The results of diagnostic right and left heart catheterization were as follows: The pulmonary capillary wedge pressure was normal (*V* 8, *Y* 3, mean 5 mm Hg). The pressures in the main pulmonary artery and venous ventricle were 20/5 and 25/2 mm Hg, respectively, and right atrial mean pressure was 2 mm Hg. A small gradient between the systemic ventricle and aorta was recorded (respective pressures 130/3 and 115/70 mm Hg). The oxygen saturation levels in the main pulmonary artery, right atrium and superior vena cava were 75, 72 and 72 percent in that order. The cardiac output was 6.7 liters/min and the cardiac index 3.4 liters/min per m^2. Biplane ventricular angiograms (Fig. 2) confirmed the diagnosis of congenitally corrected transposition of the great vessels.

Methods

After fully informed consent was obtained from both the patient and his parents, right heart catheterization was performed with the patient in the postabsorptive, nonmedicated state. A tripolar electrode catheter was positioned in the usual position (as judged from an anteroposterior view) to record the bundle of His electrograms as previously described.[7] Quadripolar and bipolar electrode catheters were advanced to the right atrium and venous ventricular

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apex, respectively, and were used to pace the atrium and ventricle and to record a high right atrial electrogram.

All data were recorded on seven channel magnetic tape using a switched beam oscilloscope (Electronics for Medicine model DR-12) and later transferred to photographic recording paper run at a speed of 150 mm/sec. Time lines were inscribed at intervals of 10, 100 and 1,000 msec. Surface electrocardiographic leads and intracardiac electrograms were recorded through 0.1 to 200 and 40 to 500 hertz filtration, respectively.

Ventricular pacing was accomplished through an isolation unit using 2 msec square wave stimuli that barely exceeded diastolic threshold. Retrograde refractory periods of the His-Purkinje system were determined by the extrastimulus technique[8–10] at a constant paced ventricular cycle length of 700 msec. Post-drive escape intervals were determined by measuring the interval from the last stimulus (after 30 seconds of continuous ventricular pacing) to the onset of the first subsequent bundle of His electrogram. S_1, H_1 and V_1 represent, respectively, stimulus artifact, bundle of His and ventricular electrograms of the basic ventricular drive beats. S_2, H_2 and V_2 represent, respectively, stimulus artifact, bundle of His and ventricular electrograms of the premature ventricular beats. H-V intervals were measured from the first sharp inscription of the bundle of His electrogram to the earliest onset of ventricular depolarization as recorded on either the intracardiac

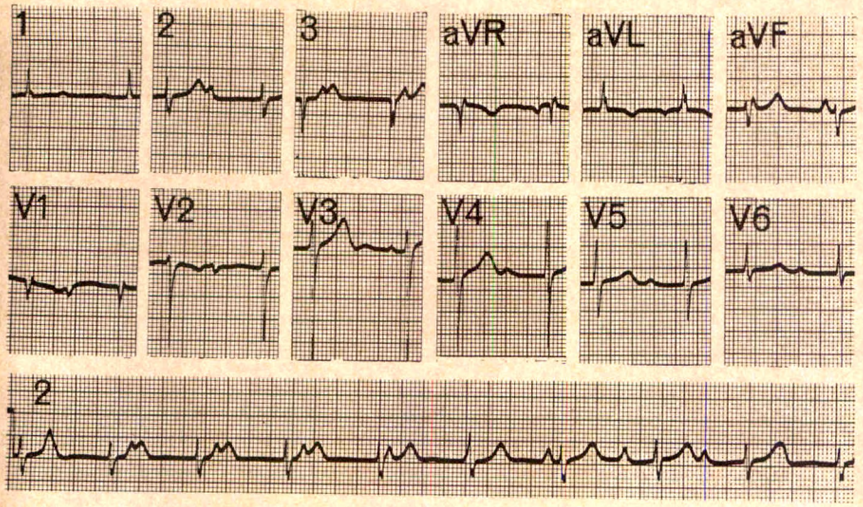

FIGURE 1. Electrocardiogram showing reversal of septal depolarization, with a Q wave in lead V_1 and absence of Q waves in leads 1, aVL, V_5 and V_6. The QRS duration is 0.08 second. The lead II (2) rhythm strip shows complete A-V block. Standardization: 1 cm = 1 mv.

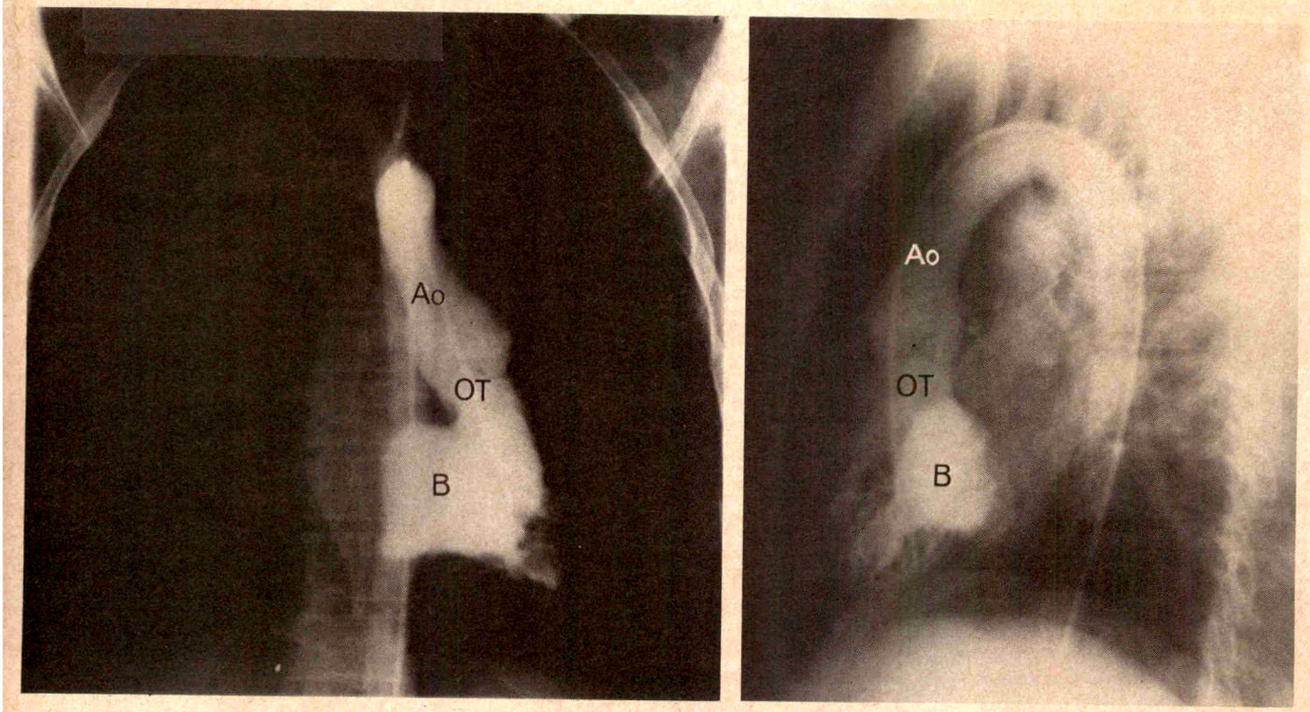

FIGURE 2. Biplane ventricular angiograms taken in the anteroposterior (**left**) and lateral (**right**) views after injection of contrast medium into the systemic ventricle. Diagnostic features of congenitally corrected transposition of the great vessels are evident: a coarsely trabeculated systemic ventricular chamber with a separate body (B) and outflow tract (OT) that ejects into an anterior aorta (Ao) forming the left border of the upper cardiac silhouette.

electrogram or the surface electrocardiogram. S_2-H_2 intervals were measured from the ventricular premature stimulus to the onset of the first sharp inscription of the bundle of His electrogram.

Results of Electrophysiologic Evaluation

Complete bidirectional A-V block was present at all times (Fig. 3). Spontaneous atrial and ventricular rates are presented in Table I, as are the responses of the spontaneous rhythm and post-drive escape intervals to carotid sinus massage, administration of atropine and isometric and treadmill exercise. On one occasion, for approximately 10 seconds the spontaneous ventricular rate slowed markedly to 43/min (cycle length 1,390 msec) without concurrent slowing of the atrial rate, change in the QRS configuration or temporal proximity to pacing, carotid sinus massage or exercise.

Bundle of His electrogram: Each ventricular complex was preceded by a bundle of His electrogram, with an H-V interval of 35 msec. The following observations suggest that this electrogram represented depolarization of the bundle of His rather than a bundle branch potential: (1) A large atrial electrogram was recorded from the same electrodes used to record the bundle of His electrogram; (2) the H-V interval was within the normal range for our laboratory (35 to 55 msec); and (3) extensive manipulation of the catheter failed to reveal an earlier bundle of His electrogram.

Ventricular pacing: Ventricular pacing from the venous ventricular apex (Fig. 3, lower panel) was performed at rates ranging from 80 to 162/min (cycle length to 370 msec). Retrograde conduction to the atria did not occur at any paced ventricular rate. Post-drive escape intervals ranged from 975 to 1245 msec, with no relation between escape interval and paced ventricular cycle length. The escape beat always originated from the bundle of His.

Retrograde refractory period studies: During these studies (Fig. 4) the His bundle deflection could be identified consistently within the ventricular electrogram of the basic

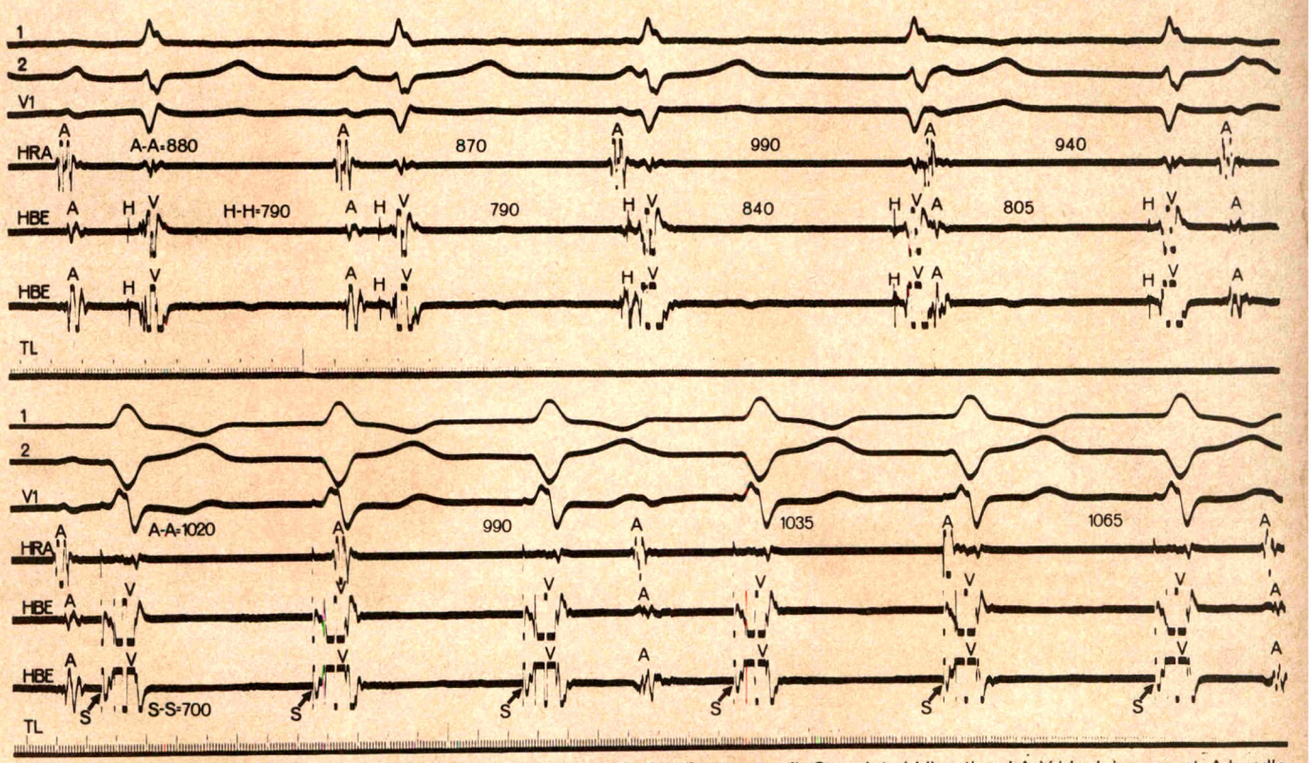

FIGURE 3. Spontaneous rhythm (**upper panel**) and paced ventricular rhythm (**lower panel**). Complete bidirectional A-V block is present. A bundle of His electrogram (H) precedes each ventricular electrogram (V) by an H-V interval of 35 msec. Time lines (TL) represent intervals of 10 msec. A = atrial electrogram; HBE = His bundle electrogram tracing; HRA = high right atrial tracing; 1, 2, V_1 = standard electrocardiographic leads; S = stimulus artifact.

TABLE I
Spontaneous Atrial and Ventricular Cycle Lengths and Response to Specific Interventions (values in msec)

	Spontaneous Rhythm	Carotid Sinus Massage		Isometric Handgrip Exercise		Administration of Atropine		Treadmill Exercise	
		Before	During	Before	During	Before	During	Before	During
Atrial cycle length	700–1100; (55–85 bpm)	750	1040	810	730	1100	620	750; (80 bpm)	400; (150 bpm)
Ventricular cycle length	800–850; (70–75 bpm)	835	970	815	715	840	575	810; (74 bpm)	440; (136 bpm)
Post-drive escape intervals	. . .	. . .	. . .	. . .	. . .	975–1245	690–800	. . .	. . .

bpm = beats per minute.

ventricular drive beats (H_1). At an interval of 400 msec between the eighth basic drive stimulus and the premature stimulus (S_1-S_2 interval), the bundle of His electrogram (H_2) merged into the ventricular electrogram from its early position indicating a retrograde relative refractory period of 400 msec (Fig. 4A). At a shorter S_1-S_2 interval of 370 msec, H_2 closely followed the ventricular electrogram, with an S_2-H_2 interval of 140 msec (Fig. 4B). At shorter S_1-S_2 intervals (350 to 330 msec), the S_2-H_2 interval lengthened further and was followed by another ventricular depolarization (V_3) (Fig. 4C). The occurrence of V_3 after marked retrograde conduction delay in the His-Purkinje system represented a form of reentry in the His-Purkinje system.[10] Reentry in the His-Purkinje system occurred consistently within a narrow zone of S_1-S_2 intervals ranging between 350 and 330 msec. Retrograde block between the ventricle and bundle of His occurred at an S_1-S_2 interval of 320 msec, which represented the retrograde effective refractory period of the His-Purkinje system (Fig. 4D).

Discussion

This is probably the first instance in which complete bidirectional A-V block in a patient with congenitally corrected transposition of the great vessels has been

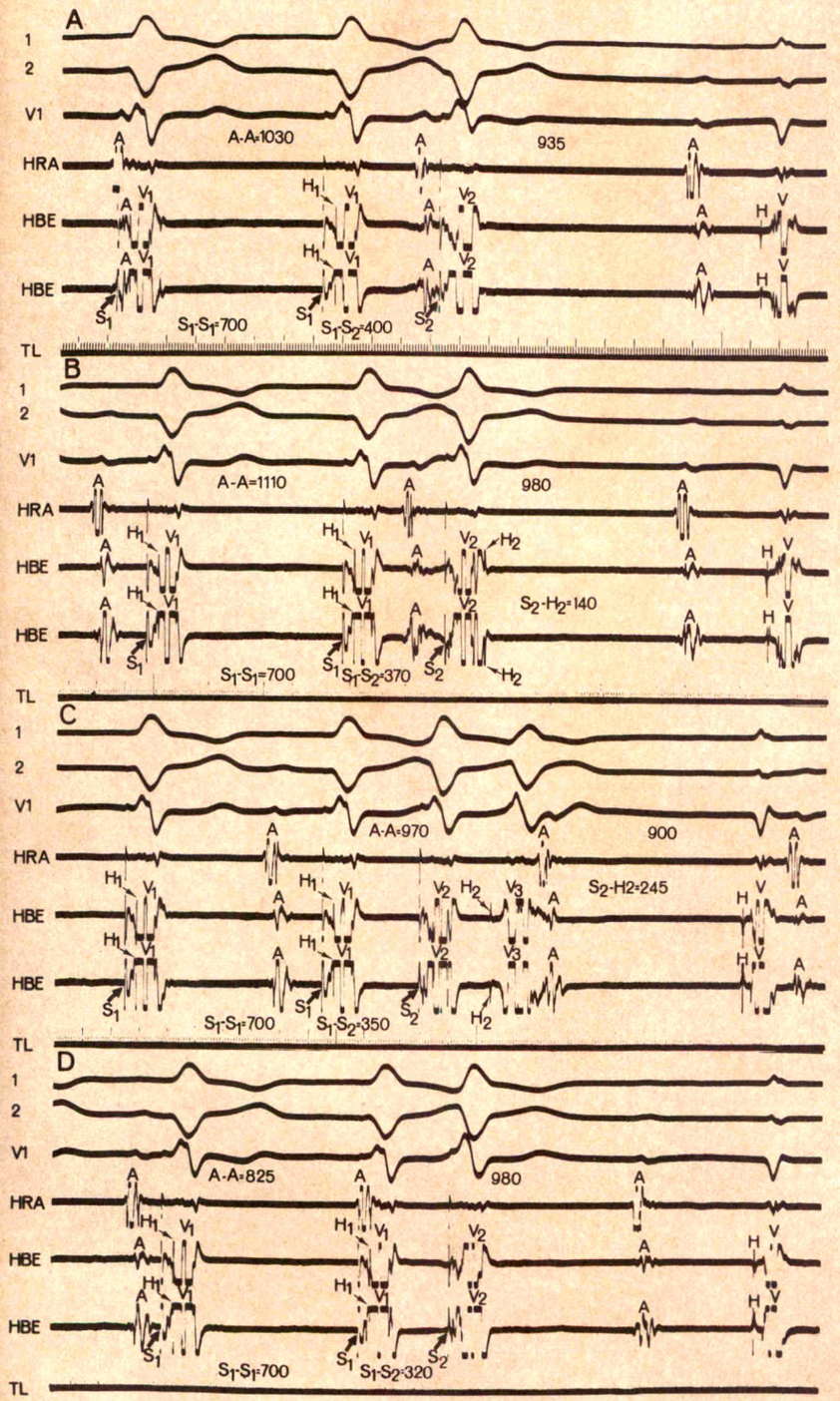

FIGURE 4. Retrograde refractory periods, illustrating reentry within the His-Purkinje system. The basic ventricular cycle length (S_1-S_1) is constant at 700 msec in all panels. The retrograde His bundle potential during the basic ventricular drive (H_1) is identifiable (a sharp biphasic deflection that precedes the local ventricular electrogram) and the S_1-H_1 interval measures 40 msec. **Panel A,** a premature ventricular stimulus (S_2) is delivered at an S_1-S_2 interval of 400 msec and H_2 merges into the ventricular electrogram (V_2), indicating that the retrograde relative refractory period of the His-Purkinje system has been reached. **Panel B,** when the S_1-S_2 interval is decreased to 370 msec, conduction to the bundle of His is delayed further (S_2-H_2 interval 140 msec) and H_2 appears after V_2. **Panel C,** at an S_1-S_2 interval of 350 msec, the S_2-H_2 interval increases to 245 msec and is followed by another ventricular beat (V_3) that is morphologically similar to V_2 in the electrocardiographic leads and is preceded by a His bundle deflection. See text for details. **Panel D,** at an S_1-S_2 interval of 320 msec, the premature impulse does not conduct to the bundle of His and no H_2 occurs after V_2, indicating that the retrograde effective refractory period of the His-Purkinje system has been reached. Note also the absence of V_3 when V_2 blocks in retrograde fashion below the bundle of His. Abbreviations as in Figure 3.

electrophysiologically localized to a site proximal to the bundle of His. Previously reported electrophysiologic studies of three patients with congenitally corrected transposition of the great vessels and first degree A-V block (two patients) or normal P-R interval (one patient) have suggested conduction delay within[4] or proximal to[5] the bundle of His. Recording directly from the proximal His-Purkinje system during cardiac surgery in an additional two patients with congenitally corrected transposition of the great vessels and preoperative first degree A-V block showed normal conduction time from the recording site to ventricle in both and delay proximal to the recording site in one.[6] Thus, electrophysiologic data in congenitally corrected transposition of the great vessels reported to date show conduction delay within or proximal to the bundle of His. Our case documents the occurrence of complete A-V block proximal to the bundle of His.

His-Purkinje reentry: The occurrence of reentry in the His-Purkinje system in our patient is of interest because of the inverted relation of the bundle branches in congenitally corrected transposition of the great vessels, in which the left bundle branch lies on the right and the right bundle branch lies on the left side of the interventricular septum.[11–13] The similarity of V_3 to the paced ventricular complexes implies that reentry in the His-Purkinje system occurred by the usual mechanism[10] despite the inversion of the bundle branches. This suggests that this type of reentry depends not on different electrophysiologic characteristics of the bundle branch, but on the proximity of the ventricular pacing electrode to the bundle branch. The occurrence of this form of reentry in the His-Purkinje system also demonstrates electrophysiologically the functional and, presumably, anatomic continuity of the bundle of His with both bundle branches, a continuity also suggested by the normal QRS duration.

Anatomic correlations: Recent pathologic studies provide an anatomic correlation for the reported electrophysiologic observations in congenitally corrected transposition of the great vessels.[11–14] Twelve of 14 hearts examined contained an "anterior [A-V] conduction system," consisting of an "anterior [A-V] node" in the anterolateral wall of the right atrium near its junction with the interatrial septum and an "anterior bundle of His" extending across the anterior subendocardial surface of the venous ventricle to the anterior margin of the membranous septum or, in eight cases, the anterior margin of an associated ventricular septal defect. An additional A-V node, usually hypoplastic, was also present in the usual A-V nodal location, but connected with the ventricle in only one case. In the two case reports in which an anterior A-V conduction system was not described,[11–14] the dissection may not have included the tissue that would contain an anterior bundle of His and A-V node.

A-V nodal versus junctional and His bundle rhythms: In each of the five pathologic cases with prior nonsurgical complete A-V block there was extensive fibrosis within the anterior bundle of His and at its junction with the anterior A-V node.[13] Therefore, the spontaneous rhythms in these cases must have originated within or distal to the bundle of His. Some investigators[15] maintain that the rate of spontaneous rhythms of bundle of His origin is not responsive to vagal influences, a responsiveness restricted to junctional rhythms of A-V nodal origin. Others[16] claim that the A-V node lacks automaticity and is not the origin of junctional rhythms. If the pathologic disruption in our case was similar to that in the five cases cited, the spontaneous rhythm must have originated in the bundle of His. The responsiveness of the rate of bundle of His discharge to carotid sinus massage and atropine in our case suggests that bundle of His rhythms in other patients may also be susceptible to vagal influences and that vagal maneuvers may not reliably differentiate between junctional rhythms of bundle of His and A-V nodal origin.

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Pathologic Correlations in a Case of Complete Heart Block With Split His Potentials Resulting From a Stab Wound of the Heart

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A 23 year old previously healthy man was stabbed in the anterior chest. This resulted in a ventricular septal defect and complete atrioventricular (A-V) block. The electrocardiogram revealed complete A-V block with a QRS pattern of right bundle branch block. His bundle recordings 26 days later revealed A-V dissociation with split His potentials ($P\text{-}H_1$ interval of 100 msec and $H_2\text{-}V$ interval of 40 msec). During the study the escape QRS shifted from right to left bundle branch block with H_2 potentials still preceding each QRS interval with $H_2\text{-}V$ intervals of 40 msec. A permanent pacemaker was implanted because of persistent congestive heart failure and bradycardia due to A-V block. The patient subsequently became asymptomatic. He died suddenly 3 1/2 years later.

Pathologically there were sizable openings in both the tricuspid and mitral valve substance and a ventricular septal defect involving the pars membranacea and part of the adjacent muscular septum. Serial sections of the conduction system revealed total destruction and fibrous replacement of the bifurcation and beginning of the right and left bundle branches and subtotal fibrous replacement of the branching bundle. Thus, the bifurcation of the bundle of His was totally absent at autopsy despite apparent electrophysiologic evidence of its existence 26 days after the stab wound. A possible explanation for this discrepancy is the subsequent fibrosis of the bifurcation produced by hemodynamic changes at the lower margin of the ventricular septal defect.

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Results of serial section study of the conduction system have been reported in only two patients with split His bundle potentials (His bundle block).[1] There are no reported histopathologic correlations regarding site of heart block due to penetrating trauma. This report concerns a patient with a knife wound of the chest with resultant heart block.[2] Electrophysiologic studies localized the area of block to the His bundle. Autopsy studies 3 1/2 years later are correlated with the electrocardiographic and His bundle findings, and a seeming discrepancy between the electrophysiologic and pathologic data is discussed.

Clinical Data

This case has previously been reported in detail[2,3] and will only be summarized here. The patient, a 23 year old man, heretofore in good health, was hospitalized at Cook County Hospital on May 23, 1971 after a knife wound to the chest. Emergency thoracotomy was performed because of cardiac tamponade, and a puncture wound of the right ventricle was closed. Atrioventricular (A-V) dissociation was noted in the operating room, and epicardial wires were implanted for temporary pacing. During the postoperative period, the patient's pulse rate remained between 40 and 50/min in the absence of pacing. Electrocardiograms revealed complete A-V block with a wide QRS escape rhythm and a pattern of right bundle branch block (Fig. 1). On May 28, a grade 4/6 holosystolic murmur was noted at the left sternal border. Diagnostic right and left heart catheter-

ization, performed on June 17 (26 days after the knife wound), demonstrated a 1.3:1 left to right shunt at the ventricular level. Elevated left ventricular end-diastolic pressure and moderate mitral insufficiency were also noted. A permanent transvenous pacemaker was implanted on July 28 because of persistent congestive heart failure and bradycardia due to A-V block. The subsequent clinical course was uneventful, and the patient returned to work without symptoms.

All subsequent electrocardiograms revealed pacemaker rhythm. Elective generator replacement was performed 2 years later, on July 24, 1973, without complication. Although progressive cardiomegaly was noted on subsequent chest X-ray films and physical examinations, the patient had no symptoms of congestive heart failure (New York Heart Association functional class 1) and was therefore not considered a candidate for mitral valve surgery. He died suddenly while working on January 21, 1975, approximately 3 1/2 years after penetrating cardiac trauma. Postmortem studies revealed normal function of the pacemaker and pacing electrode.

Electrophysiologic Studies

His bundle and left bundle branch recordings were obtained at the time of diagnostic cardiac catheterization on June 17, 1971. Control recordings revealed complete A-V dissociation with an atrial rate of 115/min and a ventricular rate of 50/min (Fig. 2 and 3A). QRS complexes were 140 msec in duration and had a pattern of right bundle branch block. Split His bundle potentials were recorded. The proximal His potentials (H_1) followed each P wave with a P-H_1 interval of 100 msec (normal P-H interval 80 to 140 msec). The distal His bundle potential (H_2) preceded each QRS complex with an H_2-V interval of 40 msec (normal H-V interval 31 to 55 msec). These findings suggested a site of block within the His bundle.

Left bundle branch potentials (LB) were recorded and were noted to occur 15 msec after H_2 and 25 msec before the QRS interval (Fig. 2). Thus the H_2-LB interval was 15 msec and the

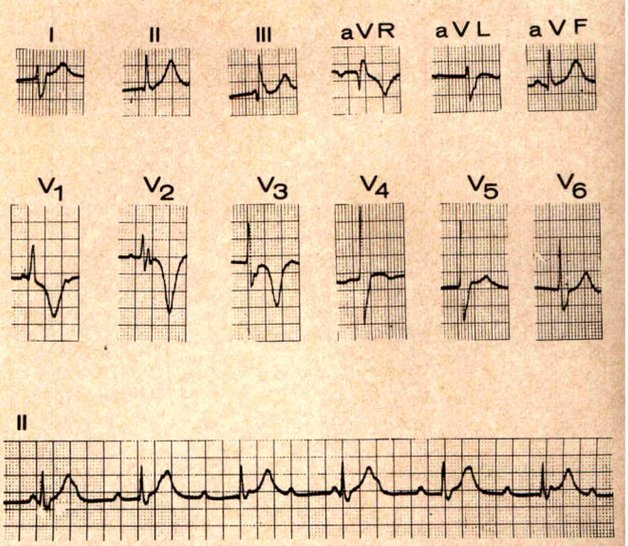
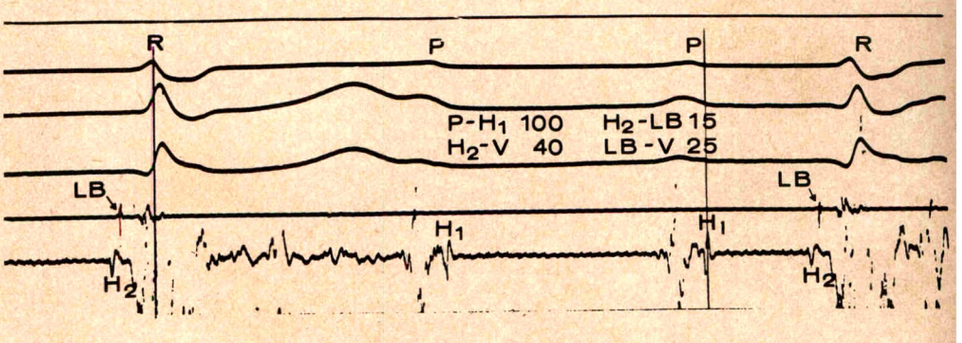


FIGURE 1. Electrocardiogram demonstrating complete A-V block with escape rhythm and a pattern of right bundle branch block. (Reprinted from Rosen et al.[2])

FIGURE 2. His bundle and left bundle branch recordings during A-V block. Shown in descending order are leads I, II and III, left bundle electrogram and His bundle electrogram. H_1 and H_2 = proximal and distal His potentials, respectively; LB = left bundle potential; P = P waves; R = QRS complex. Note complete block distal to H_1. The activation sequence of escape beats is H_2 followed by LB and QRS. Intervals are listed. Time lines are at 1 second and paper speed is 200 mm/sec. (Modified from Rosen et al.[2])



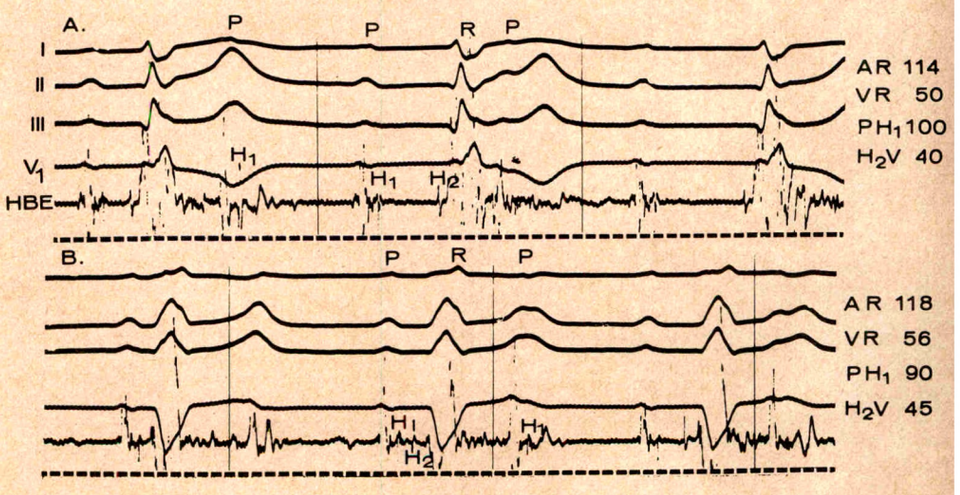


FIGURE 3. His bundle electrograms demonstrating heart block with split H potentials and escape beats with a pattern of both right **(Panel A)** and left **(Panel B)** bundle branch block. **Panel B** was recorded after infusion of isoproterenol. Note constant H_2-V intervals with both escape rhythms. Paper speed is 100 mm/sec. Abbreviations as in Figure 2. (Modified from Rosen et al.[2])

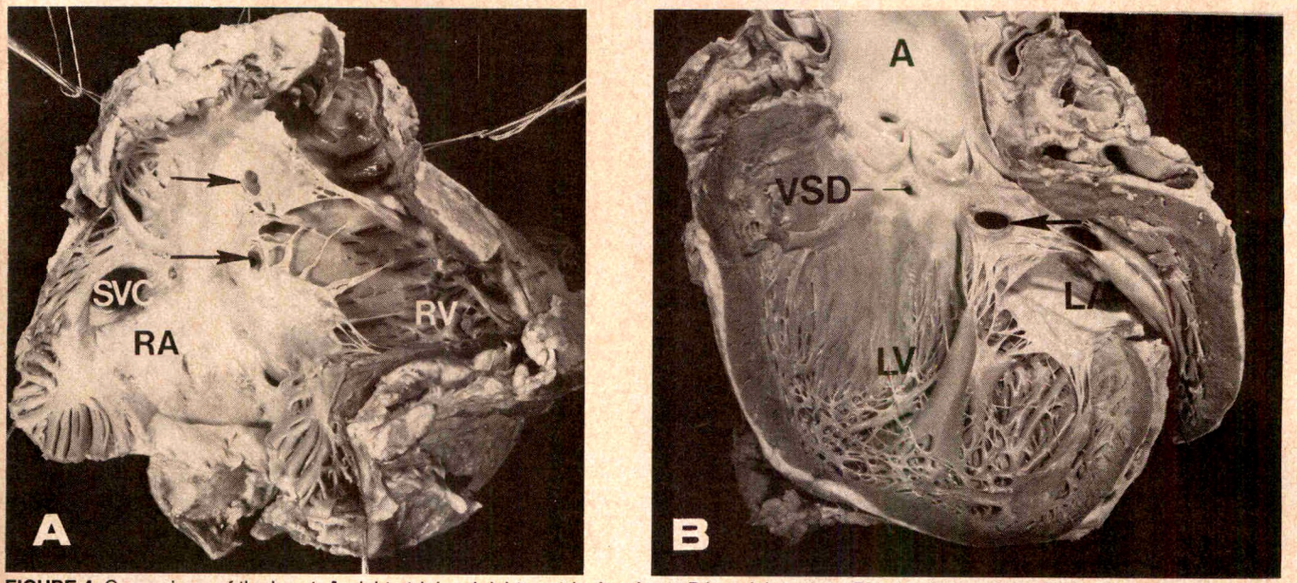


FIGURE 4. Gross views of the heart. **A,** right atrial and right ventricular views. RA = right atrium; RV = right ventricle; SVC = superior vena cava. **Arrows** point to the openings in the anterior and medial tricuspid valve produced by the knife. The ventricular septal defect can be visualized in one opening. **B,** left ventricular view. A = aorta; LA = left atrium; LV = left ventricle; VSD = ventricular septal defect produced by the knife. **Arrow** points to the opening in the anterior leaflet of the mitral valve produced by the knife. Note the thickening of the endocardium around the ventricular septal defect extending over the summit of the ventricular septum.

LB-V interval 25 msec. Both intervals were within the range of normal values previously described.[4] The sequence of H_2 and LB potentials, with a QRS pattern of right bundle branch block, suggested a His bundle rhythm with either preferential left bundle branch conduction or additional right bundle branch block.

The P-H_1 interval increased appropriately with atrial pacing, and decreased during infusion of isoproterenol and after administration of atropine. After infusion of isoproterenol, the pattern of right bundle branch block was replaced by a pattern of left bundle branch block (Fig. 3B). This change occurred without a significant change in ventricular rate or H_2-V intervals (left bundle branch potentials were no longer being recorded). After administration of atropine, the QRS configuration varied without variation in escape rate; there were periodic patterns of complete and incomplete right and left bundle branch block and some narrow QRS complexes. No premature ventricular contractions were noted.

Pathologic Findings

Examination disclosed chronic passive hyperemia of the lungs and liver and moderate pulmonary edema.

The Heart

The greatly enlarged heart weighed 680 g and hypertrophy and enlargement were manifested in all chambers. The tricuspid orifice was enlarged, and the tricuspid valve presented a defect measuring 1 cm in greatest length in the septal and anterior leaflets close to the anulus (Fig. 4A). There was a small area of fibroelastosis in the anterior wall of the right ventricle where previous sutures had apparently been placed. The mitral valve orifice was greatly enlarged, and a circular defect, about 1.5 cm in greatest dimension, was evident in the anterior leaflet of the mitral valve. The edges of this defect were greatly thickened, especially on the ventricular side (Fig. 4B). At the base of the ventricular septum was a defect measuring 0.5 by 0.4 cm in greatest dimension. This defect was situated just beneath the junction of the posterior and right aortic cusps in the region of the lower part of the pars membranacea partly involving the muscular portion of the septum (Fig. 4B). Marked endocardial thickening around the defect extended proximally over the summit of the ventricular septum. The aortic orifice and valve and the two coronary arteries were normal. The tip of the pacemaker catheter was firmly attached to the endocardium of the apical region of the right ventricle. The fibrosis around the tip was not excessive and there was no thrombus formation.

Conduction System Studies

Methods: The sinoatrial (S-A) node and its approaches were serially sectioned and every 10th section was retained. The A-V node and its approaches, the A-V bundle and the beginning of the bundle branches were serially sectioned and every fifth section was retained. The remainder of the bundle branches up to the region of the moderator band were serially sectioned and every 10th section was retained. Consecutive sections of the S-A and A-V nodes, and the A-V bundle and beginning of the bundle branches were stained with hematoxylin-eosin, Weigert-van Gieson and Gomori trichrome stains. The remainder of the bundle branches were alternately stained with hematoxylin-eosin and Weigert-van Gieson stains. In this manner 1,120 sections were examined. This manner of studying the conduction system has previously been reported.[5] The findings were controlled by the studies of aging changes,[6,7] which included study of the S-A node in three hearts of patients aged 21 to 30 years and study of the A-V node, bundle and bundle branches in four hearts of patients of similar age.

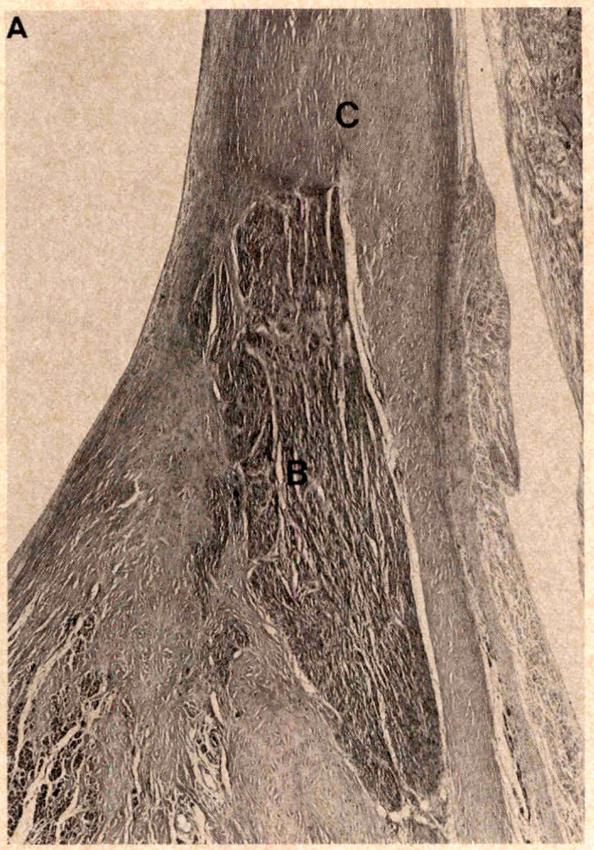
Findings:

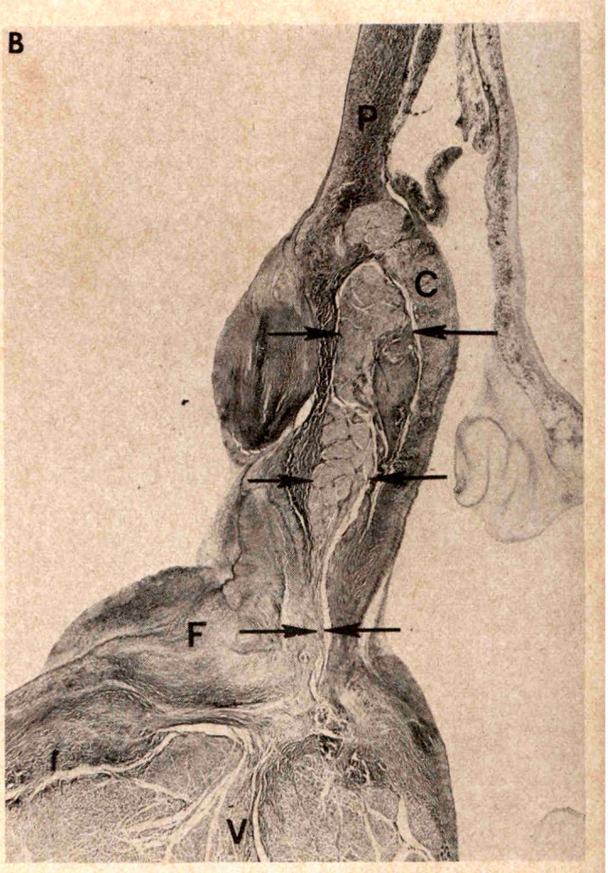
S-A node: There were no changes.

Approaches to the S-A node: Slight fibrosis was present.

Approaches to the A-V node: There was moderate fibrosis with a slight infiltration of mononuclear cells.

A-V node: Slight fibrosis was present.





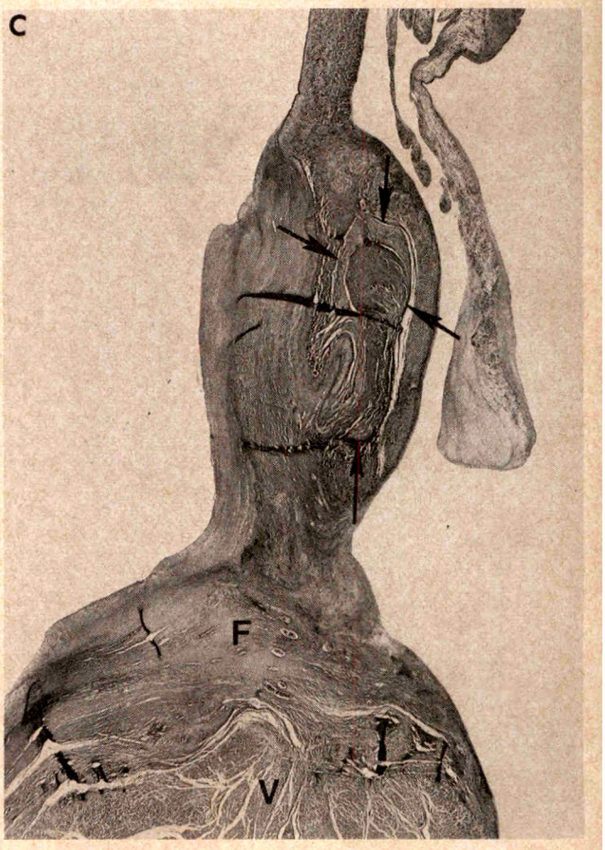


FIGURE 5. Bundle of His sections. **A,** penetrating portion of bundle (B). Note that it is intact. C = central fibrous body. **B,** proximal part of branching portion of bundle. C = conal musculature; F = fibroelastosis; P = pars membranacea; V = ventricular septum. **Arrows** point to the bundle and the beginning of the obliterated posterior fibers of the main left bundle branch. **C,** more distal portion of branching portion of the bundle **(arrows).** Only the rim of the bundle remains, the remainder being replaced by scar, and the fibers of the main left bundle branch are replaced by fibroelastosis (F). (Hematoxylin-eosin ×35 [**A**] and Weigert-van Gieson ×17 [**B** and **C**], all reduced by 30 percent.)

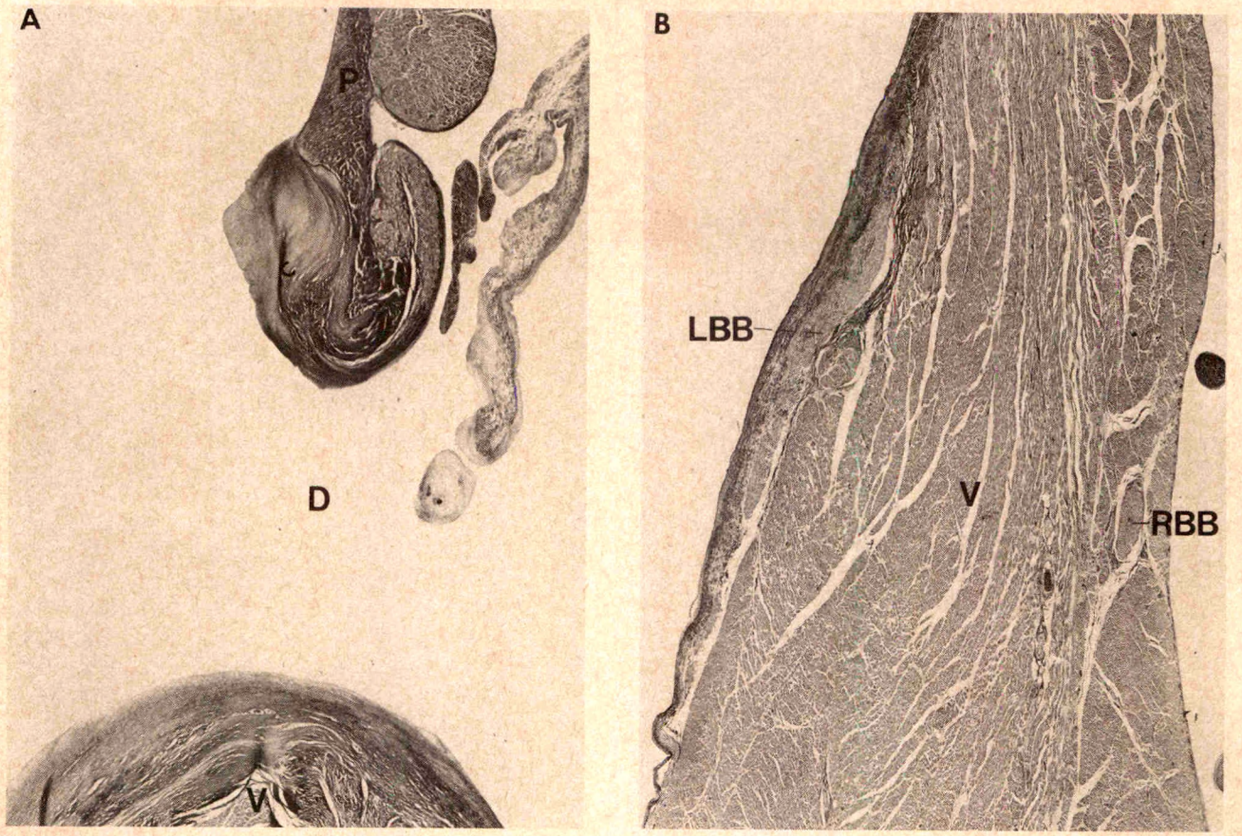


FIGURE 6. A, ventricular septal defect (D) produced by knife. In this region the bifurcation has been obliterated. P = pars membranacea; V = summit of ventricular septum with fibroelastosis. **B,** reappearance of right (RBB) and left (LBB) bundle branches. V = ventricular septum. (**A** and **B,** Weigert-van Gieson stain ×17, reduced by 30 percent.)

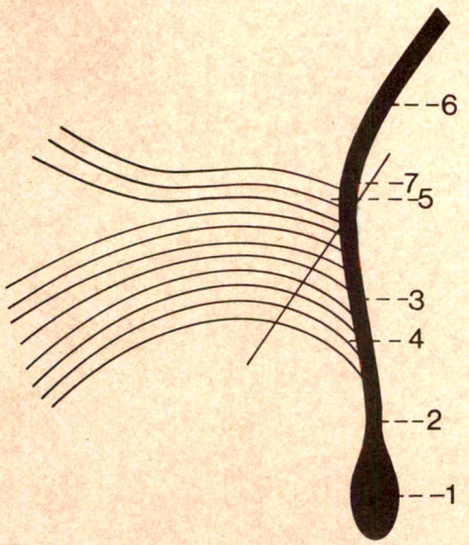


FIGURE 7. Diagrammatic sketch of part of the conduction system showing the line of destruction produced by the knife. 1 = A-V node; 2 = penetrating portion of A-V bundle; 3 = branching portion of A-V bundle; 4 = posterior fibers of left bundle branch; 5 = anterior fibers of left bundle branch; 6 = right bundle branch. Line passing through the structures indicates the line of cleavage produced by the knife.

A-V bundle, penetrating portion: In the beginning portion, there were no changes (Fig. 5A); in the distal portion, there was moderate fibrosis.

A-V bundle, branching portion: In the beginning of its course, there was moderate fibrosis (Fib. 5B). Progressively the bundle became more fibrosed until only a small rim remained superiorly (Fig. 5C). The inferior portion was enveloped in fibroelastosis. In the region of the ventricular septal defect, no bifurcation was evident (Fig. 6A). The severe fibroelastosis lay proximal to and in the region of the defect.

Right and left bundle branches: The most proximal portions of the right and the main left bundle branches were absent being replaced by fibroelastosis. In the midst of fibrous tissue, fibers of the right and left bundle branch appeared showing some fibrosis, and then they were normal more distally (Fig. 6B).

Discussion

This case is unique in that a stab wound had produced a ventricular septal defect and severed the region of the bifurcation of the bundle of His and the beginning of the main left bundle branch. Because the His bundle studies were performed 26 days after the event whereas the pathologic findings are related to progression of pathologic change up to 3 1/2 years, correlations between the His bundle recordings and the pathologic findings must take into account this progression.

Electrophysiologic findings: The most reasonable explanation of the electrocardiographic findings based on the electrophysiologic data obtained 26 days after injury was that the His bundle had been severed, resulting in distal His bundle escape rhythm.[2] Longitudinal dissociation in the bifurcating portion of the bundle (distal His bundle) allowed preferential distribution of the cardiac impulse to one or the other ventricle. Both bundle branches appeared capable of conduction. A pattern of right bundle branch block appeared to reflect preferential conduction to the left bundle branch, while a pattern of left bundle branch block reflected either a shift in pacemaker location in the distal His bundle or a distribution of impulses down the right bundle branch. Narrow QRS complexes reflected simultaneous conduction in both bundle branches.

The proximal H_1 potential certainly reflected the electrogram generated by the penetrating portion of the His bundle and perhaps proximal branching bundle. Block occurred in the branching portion of the His bundle that was partially destroyed. We cannot explain our electrophysiologic findings without postulating some continuity between the right and left bundle branches in or close to the bifurcation at the time of the His bundle studies. Without some continuity H_2 could not have occurred with a normal constant H_2-V interval before beats that had a pattern of both right and left bundle branch block. Even if one postulated that H_2 was recorded from the proximal right bundle branch, this potential could not occur with beats conducted with a pattern of right bundle branch block unless there was some continuity between the proximal right and left bundles.

Pathologic findings: To understand our pathologic findings the anatomy of the normal conduction system should be taken into account (Fig. 7).[8] The penetrating bundle passes through the central fibrous body and sometimes through the atrioventricular part of the pars membranacea. As the bundle reaches the interventricular part of the pars membranacea it begins to give off fibers destined for the posterior radiation of the left bundle branch, thus becoming the branching portion of the bundle. In most cases all of the fibers destined for the posterior radiation are given off before the bifurcation into the right bundle branch and remaining fibers of the left bundle branch. This point has not been sufficiently stressed by others.[9] The left bundle branch is given off beneath the posterior aortic cusp and the bifurcation occurs at a point proximal to or at the level of the commissure between the right and posterior aortic cusps.

Thus, in our case the knife had passed through the interventricular portion of the pars membranacea producing a ventricular septal defect as well as interrupting the branching portion of the bundle of His in the region of the bifurcation. Since A-V block occurred, an obliquity of severance ensued, resulting in the severance of the entire beginning portion of the left bundle branch with the bifurcation (Fig. 4B and 7). Had only the bifurcation been interrupted, right bundle branch block with left axis deviation would have ensued. At the time of autopsy, 3 1/2 years later, the bifurcation and the entire beginning portion of both bundle branches were not present. However, marked fibroelastosis in this region, adjacent to the ventricular septal defect and extending over the summit of the ventricular septum, was probably produced by hemodynamic changes about the septal defect and healing of the knife wound. Thus, it is likely that a portion of the bifurcation was still present at the time of the electrophysiologic studies but that it had become fibrosed in the course of time.

We do not know the cause of sudden death in this patient. A contributing factor was the mitral insufficiency created by the stab wound.

Acknowledgment

We are indebted to Mrs. Mildred M. Travers for technical assistance and to Mrs. Jo Price and Mrs. Florence Jacobson for assistance in the preparation of this paper.

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Computer Analysis of the Electrocardiogram

CHARLES A. BERTRAND, MD, FACC

White Plains, New York

The comprehensive review by Caceres[1] in this issue of the Journal touches on all of the major contributions in the relatively new field of computer electrocardiography. He writes of $220 million worth of computer systems and $135 million of related terminals to be purchased by 1980 and of further annual expenditures in excess of $200 million. Thus, there is an obvious need not only to evaluate the current status of computer electrocardiography but also to obtain some idea of its future use.

Several more or less independent procedures are needed to arrive at a computer-interpreted electrocardiogram. Initially the data are acquired by a three channel electrocardiograph that records the 12 lead electrocardiogram or three orthogonal (vector) leads, or both. Frequency modulation tape may be used for recording and storage. Since the computer deals with numbers only, an analog to digital converter is used to convert the electrocardiographic tracing or analog signal into a series of numbers or digits. Work in this area was originally done by Taback et al.,[2] and later extended by Stallman and Pipberger[3] and Caceres et al.[4] Samples of the tracing are usually taken at intervals of 2 to 4 msec. The digitized values are read into the computer and are compared with the criteria of the analysis program. One computer program is used for wave recognition. A second is used to determine wave amplitudes and durations as well as various time intervals. Still another is used for rhythm analysis, as first developed by Bonner and Schwetman in 1968 but not available for routine use at that time.[5] Actually, one structured multiphased program is used that identifies waves, performs the various measurements and analyzes rhythm and contour. Currently, most records are stored on tape or even disk, but improvements are needed, essentially for data compression or transformation into some yet to be perfected efficient storage medium. Although some comparison programs of serial tracings have been undertaken,[6] more evaluation of such programs is needed and problems of storage and retrieval must be solved. The results of the last 16 years suggest that computer analysis of electrocardiograms is good for normal tracings and less good for tracings the computer labels abnormal. Without discussing sensitivity and specificity it is reasonable to state that, in our experience, when a computer interprets an electrocardiogram as normal it has a better than 95 percent probability of being correct, allowing for minor degrees of S-T segment deviation; this figure is in agreement with the data of Crevasse and Ariet.[7] Since 1968, we have performed more than 100,000 multiphasic health testing examinations and in most subjects have recorded the electrocardiogram on tape for computer analysis. (Until July 1974 we used the Smith-Hyde vector-lead program[8] and since then have used the Bonner 12 lead program.[9]) In our experience, the computer tends to be accurate in interpreting normal tracings, but has at least a 1 in 3 chance of being partly or completely in error about tracings it labels abnormal. Yet its performance is better with some abnormal tracings. For example, when the computer interprets a left ventricular conduction disturbance or left bundle branch block, it is virtually always correct; in contrast, there is greater variability with a right ventricular conduction disturbance or right bundle branch block.

Two major limitations to computer use are implied in these considerations: First, the computer's low level of reliability in interpreting abnormal tracings limits its clinical usefulness since, in most hospitals, the majority of recorded electrocardiograms are abnormal. Second, the lack of a practical comparison program further limits routine clinical use. What then, is the present "place" of the computer in electrocardiographic interpretations?

We may consider using computer analysis of the electrocardiogram in three areas: (1) screening programs, (2) the doctor's office, and (3) in hospitals.

(*1*) *In screening programs*, the computer probably functions at its highest level. Simply expressed, the computer may be used to sort out the normal from the abnormal. We recommend that the screening be followed with a sampling review procedure (at IBM, 10 percent of normal electrocardiograms and virtually all abnormal records are reviewed by cardiologists). We have found the computer to be very helpful and have arrived at a computer-assisted type of electrocardio-

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graphic interpretation.[10] Computer analysis is of value for sorting out normal tracings, giving precise time intervals and measurements and offering various diagnostic possibilities for the cardiologist's consideration. I think, therefore, that computer analysis leads to both increased speed and increased accuracy in interpreting the electrocardiogram.

(2) *In the doctor's office*, there is a greater degree of variability. Ideally, a doctor who takes an electrocardiogram should be qualified to interpret it; if not, some other doctor or facility should be available for interpretation. Probably computer interpretation of the electrocardiogram has little practical application for the qualified physician who has a low to moderate volume of electrocardiograms to interpret. It may be more useful to the unqualified doctor, or for the doctor in a remote area where facilities for interpretation are not available. For example, telephone transmission of the electrocardiogram to a computer center may be utilized, with the interpretation relayed back to the attending physician.

(3) *Among hospitals*, paradoxically, both the smallest and the largest institutions appear to be best suited for computer interpretation of electrocardiograms. The smallest hospitals are suitable because they may have no cardiologist available to interpret the tracings; in such a case, the electrocardiogram may be transmitted to a center by telephone line. Larger hospitals may have so large a volume of electrocardiograms that computer use is cost-justified. Intermediate-sized hospitals probably represent the exception because, presumably, they have qualified physicians available to interpret the electrocardiograms and the volume of tracings in most of these hospitals is probably insufficient to justify the cost of computers. For hospitals of all sizes, lack of a comparison program presents problems since not only are many electrocardiograms abnormal, but also in many hospitalized patients serial electrocardiograms are taken, thus further limiting the usefulness of computer interpretation. Furthermore, patients may be nervous or seriously ill, have tremors or postoperative bandages, or have other factors that could cause the recording of any electrocardiogram (and therefore input to the computer) to be suboptimal.

Prospects for the future: Within 5 years I believe there will be a major development—considerable use of the "stand-alone" unit, that is, a simple box containing a three channel electrocardiograph with an analog to digital converter to digitize the electrocardiographic signal and a dedicated minicomputer whose sole function will be to interpret the electrocardiogram. I can envision a 12 lead or a 3 orthogonal lead electrocardiogram with the interpretation printed on the tracing itself. This unit may be adequate for one tracing, but what about the complicated cases in which one tracing is abnormal and serial tracings are required? And what about physician review? Herein lies the major problem!

Unless, and until, a practical, reliable comparison program is available and has been well tested and validated, the potential of computer interpretation of the electrocardiogram will be sharply limited. Instead of using "stand-alone units," one may transmit the electrocardiographic signals directly to a computer center for processing or use a stand-alone unit with provision for transmitting to a computer center, thus allowing greater flexibility; but a comparison program will still be required. When the comparison and storage-retrieval problems have been resolved, we may then anticipate other problems, such as regionalization, possible use of Social Security numbers for identification, use of data banks and problems of program evaluation and selection (which program or programs to use and how to validate them). Other problems—those associated with use of the computer in exercise testing and rights of privacy of the patient—loom just over the horizon.

Nonetheless, I believe that miniaturization will progress, a practical comparison program will be developed, extensive data banks will be established, and many other problems will be resolved, but the solutions will take years to accomplish. A competent cardiologist will always be needed to interpret the abnormal electrocardiogram. I doubt that the accuracy of the computer will ever be sufficiently great to permit its unaided use in interpreting a difficult arrhythmia. I can also envision problems related to time in comparison of electrocardiograms, problems of correlation with clinical events in a satisfactory manner. Hence we may anticipate the continued coexistence of cardiologists and computers in, I hope, a constructive way leading to greater speed and procession of electrocardiograms but, more importantly, ultimately to a higher quality of interpretation.

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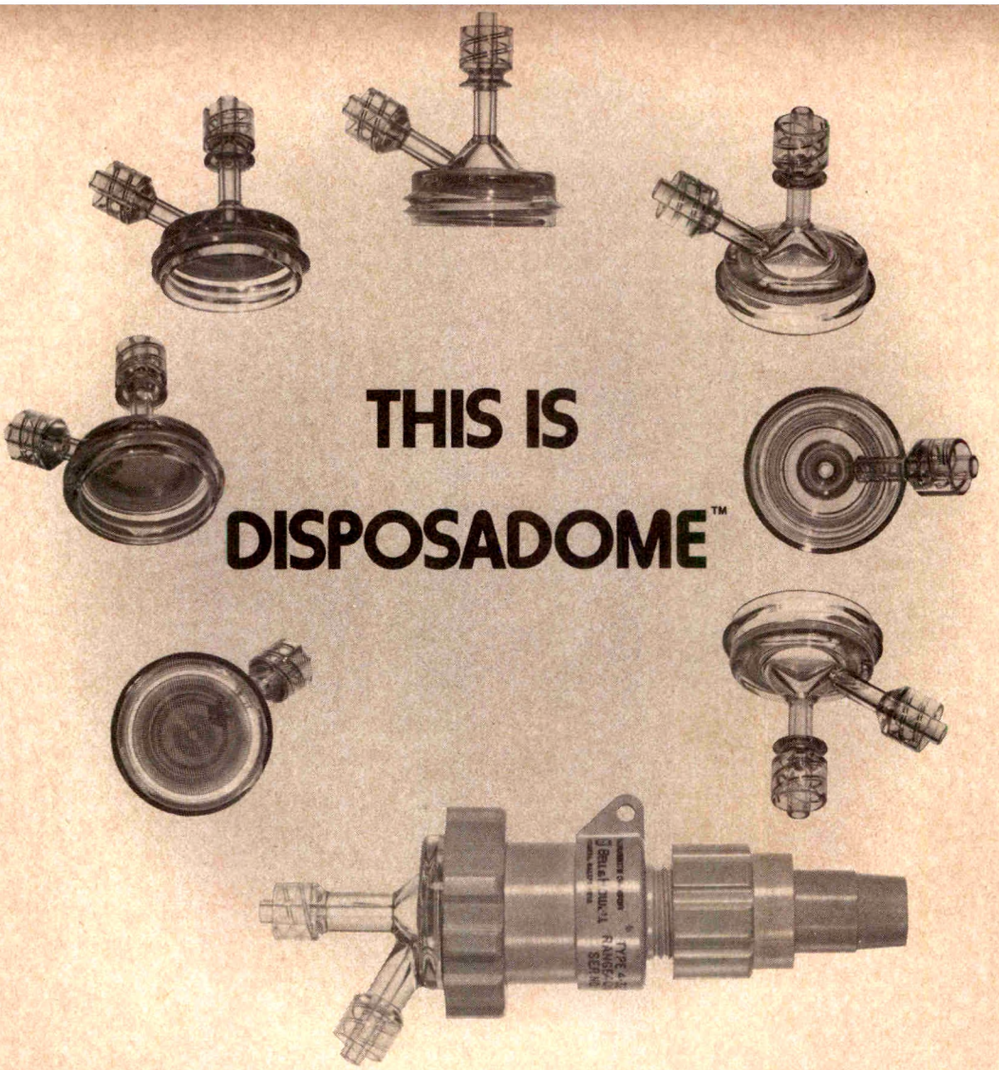

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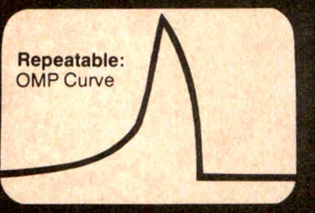

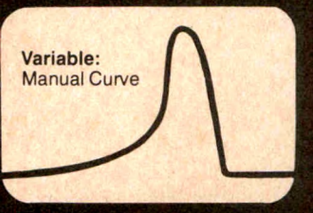

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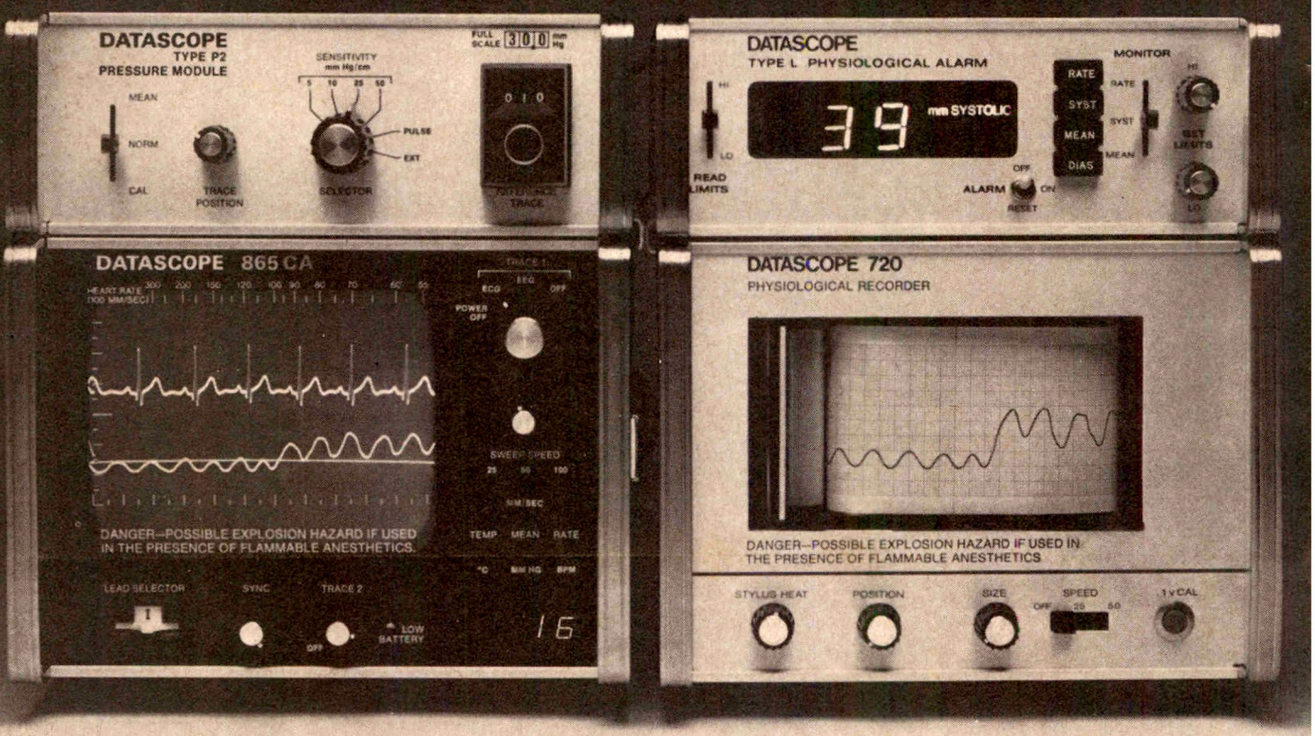

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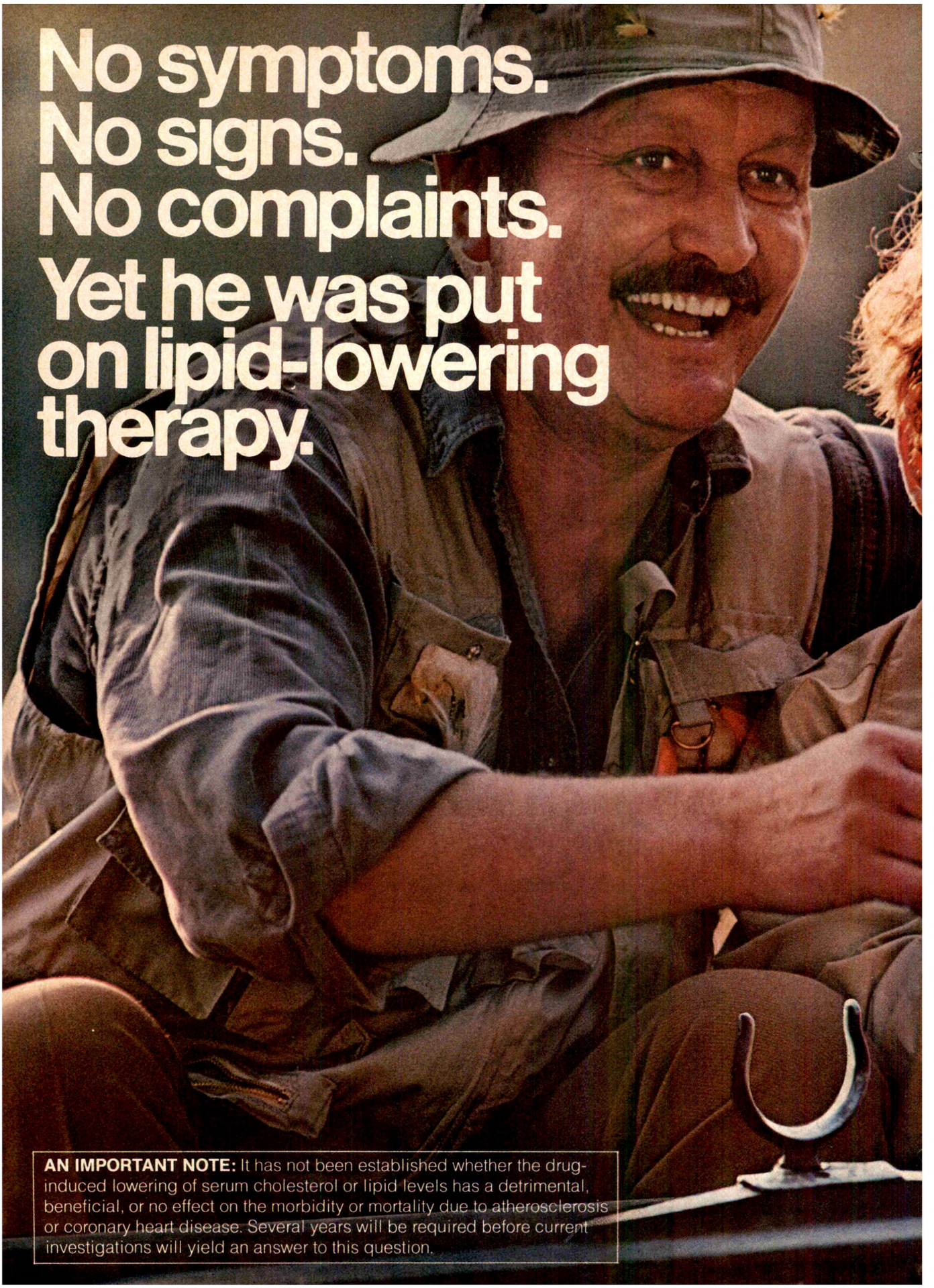
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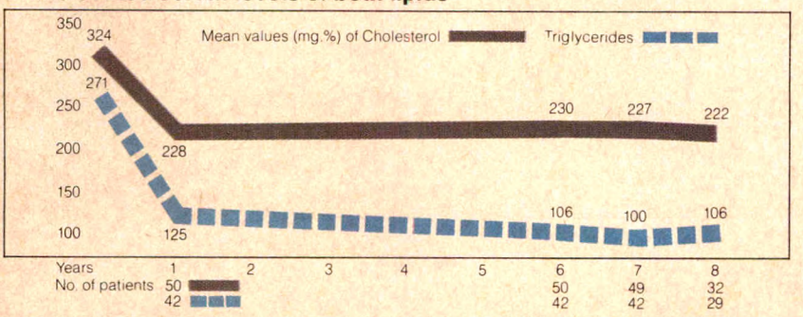
You cannot change your patient's heredity. Or sex. Or age. But you can help alter other factors in his profile: improper diet, excessive smoking, hypertension *and* hyperlipidemia. While diet is the starting point in the management of primary hyperlipidemia, it is not always successful. As Zelis[2] points out: "Dietary control requires strong motivation and self-discipline that not every patient is able to exercise." And even under carefully monitored dietary regimens, lipid lowering may be inadequate. For these reasons, it is often necessary to add an antilipidemic agent such as ATROMID-S to produce significant reductions in serum lipids.

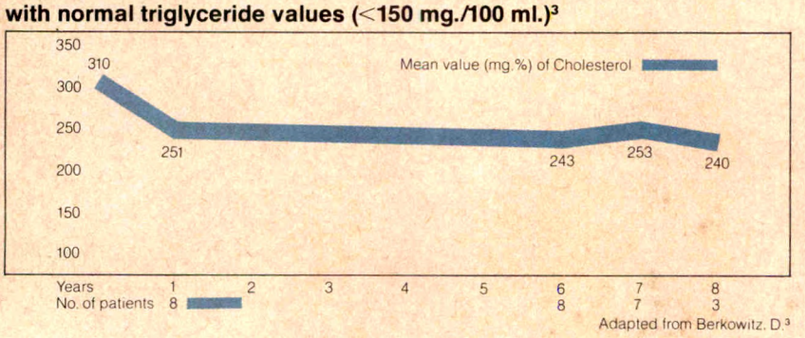
Atromid-S (clofibrate)—to help reduce elevated levels of cholesterol and/or triglycerides when diet alone is not enough

ATROMID-S as an adjunct to diet has a proved record of effectiveness in lowering elevations of both cholesterol *and* triglycerides. Lipid lowering is sustained as long as ATROMID-S treatment is uninterrupted. The drug is effective in a simple, well-accepted regimen that patients can stay with. Initial *and* maintenance dosage is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage. The lipid-lowering effect of ATROMID-S is usually noted during the first month of therapy. The higher the initial level, the greater the lipid reduction likely to occur. If response is inadequate after three months, the drug should be discontinued. However, if xanthoma tuberosum is present, treatment should be continued for longer periods (even up to one year), provided there is a reduction in the size and/or number of the xanthomas.

Significantly lowers cholesterol and triglycerides in patients with elevated serum levels of both lipids[3]



Significantly lowers elevated serum cholesterol levels in patients with normal triglyceride values (<150 mg./100 ml.)[3]



Adapted from Berkowitz, D.[3]

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS
WARNING: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Atromid-S® (clofibrate) helps control the lipid factor in your patient's profile

Initial and maintenance dosage: 2 Gm. daily (four capsules), in divided doses. Some patients may respond to a lower dosage.

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® (clofibrate)

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (Sf 20-400) rich in triglycerides than the low density lipoproteins (Sf 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur. During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These

effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 Gm. daily, in divided doses. Some patients may respond to a lower dosage.
Maintenance: Same as for initial dosage.
Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S (clofibrate). The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

References: 1. Scheig, R.: Conn. Med. 39:71 (Feb.) 1975. **2.** Zelis, R.: Clinical Focus on Hyperlipidemia: Detection and Diagnosis, Ayerst Laboratories, 1975, p. 8. **3.** Berkowitz, D.: J.A.M.A. 218:1002 (Nov. 15) 1971.

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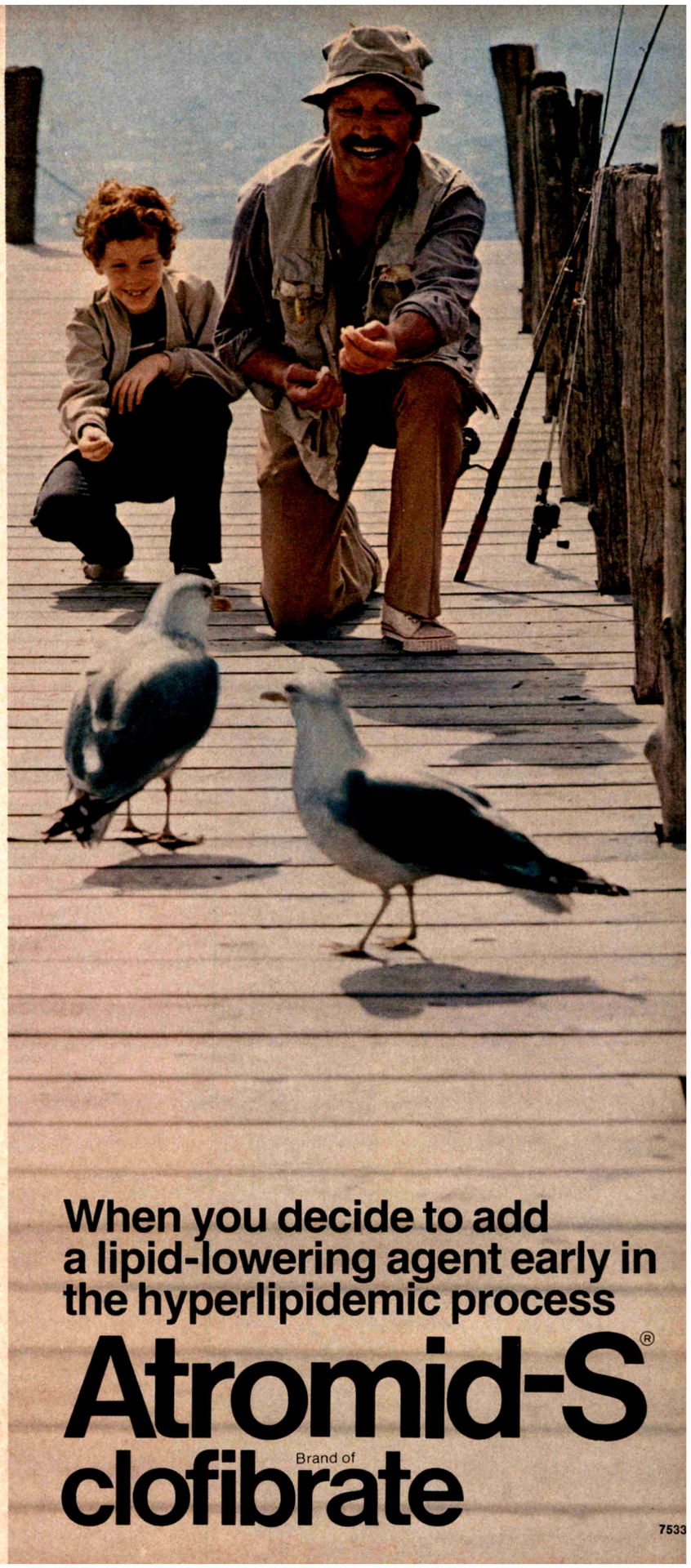


When you decide to add a lipid-lowering agent early in the hyperlipidemic process

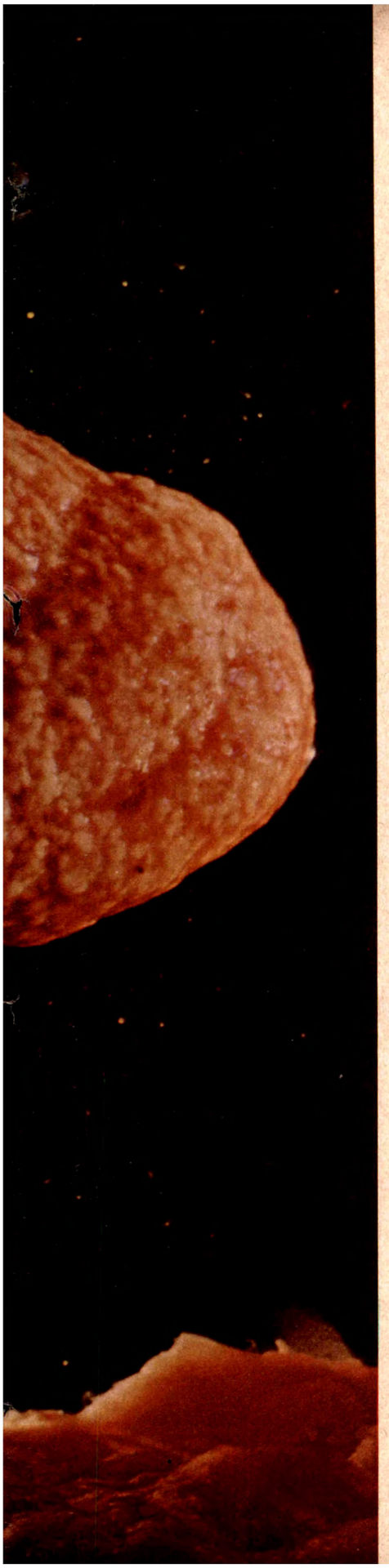
Atromid-S®

Brand of

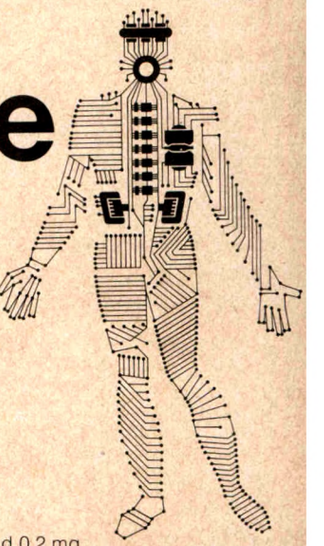
clofibrate

7533

Renal Apocalypse
It can start with a little high blood pressure
Kidney of woman, 59, severely hypertensive.
Kidney grossly scarred and contracted. Numerous
petechial hemorrhages and a cyst. Postmortem.
Photographed exclusively for Boehringer
Ingelheim by Lennart Nilsson.



Reach for normal blood pressure



In mild to moderate hypertension

Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl)

Catapres can make a diuretic look good.

When more than a diuretic is needed, adding Catapres usually lowers blood pressure more.[1]

You can add Catapres to Catapres to get pressure down near normal.

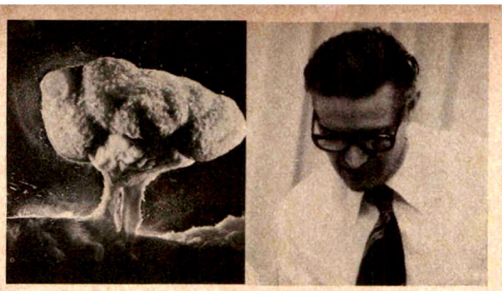
Wide therapeutic dosage range—0.2 mg to 2.4 mg* daily. Catapres may be all you need to reach near-normal levels.

*Doses as high as this have rarely been employed.

Catapres usually doesn't add a lot of problems.

The most common side effects—dry mouth, drowsiness, sedation—generally tend to diminish with time. When stopping Catapres, reduce dosage gradually over two to four days to avoid a possible rapid rise in pressure.

Please see next page of advertisement for
a brief summary of the prescribing information including precautions, warnings, and adverse reactions.



Hypertension through the lens of Lennart Nilsson. The photographic genius of Lennart Nilsson has revealed extraordinary details of the human organism. Now, Boehringer Ingelheim has commissioned an exclusive series of photographs by Nilsson depicting hypertensive damage. This series, presented in the interest of continuing medical education, vividly records the progression of an insidious disease.

In mild to moderate hypertension

The Catapres Potential: blood pressure not just down, but down near normal

Catapres® (clonidine HCl)

Tablets of 0.1 and 0.2 mg

Start with Catapres when a diuretic is wrong for your patient

Add Catapres when a diuretic alone doesn't let you reach near-normal pressure

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

Under license from Boehringer Ingelheim GmbH

Reference: 1. Data on file at Boehringer Ingelheim Ltd.

Boehringer Ingelheim Ltd.
Elmsford, New York 10523

NERVOUS SYSTEM AND INOTROPIC EFFECT OF DIGITALIS IN DOGS

Kim et al.[1] raise some interesting questions regarding the role of the nervous system in the inotropic and cardiotoxic effects of acetylstrophanthidin in dogs. They conclude that "modification of the direct inotropic effect of digitalis by the autonomic nervous system, if present, must be small." As they indicate, this observation is at variance with data from our studies[2] in which we found no significant positive inotropic effects in dogs with intact baroreceptor nerves but significant effects in dogs with denervated baroreceptors.

There were several differences between the experimental protocol of the two studies. First, all of our animals were anesthetized with chloralose, an anesthetic agent known to preserve the integrity of the cardiovascular reflexes (see references cited in Reing et al.[2]), whereas Kim et al. used pentobarbital. They indicate that some animals were given chloralose but their data were not included because the results were not different from those obtained in the animals given barbiturates. The crucial question is whether Kim et al. compared the inotropic effect of acetylstrophanthidin in chloralose-anesthetized animals with and without intact baroreceptors. Second, we measured contractile force with a strain gauge arch, whereas Kim et al. used the first derivative of left ventricular pressure (dP/dt). We have previously commented[2] on the different results that can be obtained with these methods. Third, we administered acetylstrophanthidin as a single bolus injection of 12.5 or 25 μg/kg whereas Kim et al. administered it as a bolus injection of 5 μg/kg at 5 minute intervals. Fourth, we examined the role of the nervous system by surgically denervating the reflexogenic areas whereas Kim et al. examined it by pharmacologically blocking the efferent nerves.

We also take issue with some statements made by Kim et al. First, they used our previous finding to hypothesize that "if the described reflex sympathetic withdrawal or stimulatory effect of digitalis on the sympathetic nerves were hemodynamically significant, one would expect directionally different inotropic responses depending upon the existing autonomic tone." In our dog study we did not observe directionally different inotropic changes. The only significant change that occurred was in the debuffered animals; that is, these animals had a marked increase in contractile force whereas there was no significant change in contractile force in animals with intact cardiovascular reflexes. Second, it is difficult to understand why Kim et al. referenced our studies to register concern with the role of a stimulatory effect of digitalis on sympathetic nerves when studying the effect of subarrhythmic doses of this agent on cardiovascular hemodynamics. Our studies indicate that it is the toxic arrhythmogenic dose that increases sympathetic outflow. Hence, it would not be anticipated that a stimulatory effect on sympathetic nerves would be involved in the positive inotropic effect of subarrhythmic doses of the drug. Indeed, their results are consistent with ours in that their experiments in animals pretreated with propranolol suggest that larger doses of acetylstrophanthidin can be given before toxic arrhythmias develop.

In addition, we are concerned about several aspects of the study by Kim et al. First, they do not seem to have used proper controls. That is, they appear to have compared animals anesthetized with 30 mg/kg of pentobarbital supplemented by 1.5 to 2.0 mg/kg administered every 30 minutes (Groups II and III) with animals receiving intramuscularly administered morphine, 2.5 mg/kg, followed in 30 minutes by intravenously administered pentobarbital, 15 mg/kg. Second, to determine the influence of an intervention on the inotropic response to digitalis, it would seem essential to compare the response obtained in different groups at the same dose of acetylstrophanthidin. Instead, they compared the inotropic responses to acetylstrophanthidin using a percentage of the toxic dose; thus, the toxic dose differed considerably in intact animals and in those with autonomic blockade.

Finally, it seems to us that Kim et al. should compare their results with those of investigators who have used similar experimental techniques. One example is the study of Halloran and Downing,[3] who found, using the first derivative of the left ventricular pressure, that in puppies anesthetized with pentobarbital administration of acetylstrophanthidin (20 μg/kg) produced a greater increase in contractile force in animals pretreated with a beta adrenergic blocking drug than in control animals. Similar findings were recently reported for adult dogs by the same group.[4] Examination of the results of these two studies indicates that modification of the direct inotropic effect of digitalis by the autonomic nervous system, rather than being small, is significant.

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Washington, D.C.

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2. **Reing CM, Thibodeaux H, Gillis RA, et al:** Influence of baroreceptor reflexes on cardiovascular responses of the dog to acetylstrophanthidin. J Pharmacol Exp Ther 184: 641–648, 1973
3. **Halloran KH, Downing SE:** Inotropic and toxic responses to acetylstrophanthidin in young animals: relationship of hypercapnia and beta-adrenergic blockade. J Pharmacol Exp Ther 183:146–153, 1972
4. **Halloran KH, Downing SE:** Inotropic responses to digoxin during hypoxia and autonomic blockade. Am J Physiol 229:309–313, 1975

REPLY

We agree that there are differences in the experimental design of the study of Reing et al. and ours. In our study, the cumulative dose of acetylstrophanthidin at which the experiment was terminated in each animal was not a subarrhythmic dose but a toxic arrhythmic dose. We also observed a linear dose-inotropic response relation in our chloralose-anesthetized animals. However, we did not undertake a systematic comparative study of the anesthesia in our pentobarbital- and chloralose-anesthetized groups. Although in instrumented intact dogs chloralose appears to provide hemodynamically stable preparations,[1] this information should not be extrapolated to open chest dogs as evidenced by marked differences in the heart rate and blood pressure when two studies are compared.[2,3] Chloralose has been reported to produce greatly exaggerated baroreceptor response[3–5] not only to neuroexcitatory drugs but also to pressure changes, thus suggesting that this agent may not be an ideal anesthetic when evaluation of specific drug action indirectly involves baroreceptor effects.

It is generally agreed that maximal dP/dt can reliably detect changes in contractile state if preload, afterload and heart rate are maintained constant. In our study heart rate was maintained constant and left ventricular end-diastolic pressure either remained the same or decreased after administration of acetylstrophanthidin. Although arterial pressure increased during the drug infusion, this increase would not have directly affected our results since dP/dt at 40 mm Hg of developed pressure showed the same trend as maximal dP/dt. Thus, we believe that the changes in dP/dt in our study accurately reflected changes in contractile state.

It is also essential to consider such factors when one is assessing contractile state by means of strain gauge arches.[6] When the segment of muscle beneath the feet of the strain gauge arch is stretched to 50 percent or more of its initial length, it may in fact be beyond the peak of its length-tension curve. Furthermore, at this length changes in arterial pressure and in the myocardium adjacent to the muscle segment may significantly affect the measurement of contractile force.

Changes in heart rate have a variable effect, but increases in contractile force may also be seen with increasing rate. In the study of Reing et al. heart rate was not controlled and there were significant changes in systemic arterial pressure in their debuffered animals not on bypass. In the bypassed animals, blood pressure in the debuffered group was strikingly and surprisingly much lower than in the control animals before administration of acetylstrophanthidin.

As Gillis et al. point out in their letter, they surgically denervated the reflexogenic areas, wheras we employed pharmacologic blockade. Obviously in their study the effect of circulating catecholamines on the myocardium was not blocked. This may have contributed in part to the differences in results. In our study a greater inotropic effect was observed in animals with autonomic blockade than in those without. Although this could be due in part to some sympathetic withdrawal in animals without blockade we believe that other factors are primarily responsible. First, more acetylstrophanthidin was given before toxic arrhythmias appeared in the animals with blockade. However, 75 percent of the toxic dose in these animals corresponded to the 100 percent dose in Groups 1 and 3 and yet the percent increase in dP/dt at the 75 percent dose was still greater in the animals with blockade than dP/dt at the 100 percent dose in Groups 1 and 3.

The other factor that must then be considered is the lower level of myocardial contractile state before administration of acetylstrophanthidin in the group with pharmacologic blockade. It has been well demonstrated that the magnitude of the inotropic response to digitalis is dependent upon the control level of the contractile state,[6,7] that is, the lower the basal contractile state the greater the response to digitalis. Thus, in studies of the relation between the autonomic nervous system and the inotropic effect of digitalis using beta adrenergic blocking agents, which depress basal contractile state, a greater increase in digitalis-induced inotropic effect after beta blockade need not imply that the sympathetic nervous system modified the inotropic effect of the glycoside. In the study of Halloran and Downing (Ref. 5 of Gillis et al.) a 66 percent increase in dP/dt occurred during administration of digoxin in autonomically intact animals, a finding that is not dissimilar from ours.

We emphasize that in our study each animal served as its own control and that in each group in which the mode of anesthesia was situationally appropriate to the designated autonomic status a linear inotropic response occurred during administration of acetylstrophanthidin in contrast to the effect of the drug on atrioventricular (A-V) conduction. Although this inotropic response was greater in animals with pharmacologically induced autonomic blockade than in those without such blockade, we do not believe that the autonomic system was significantly involved in the response. In contrast to the effect of acetylstrophanthidin on A-V conduction, which was certainly mediated in large part by the autonomic nervous system, the effect of digitalis was not. We agree completely with the recent editorial comments of Gillis et al.[7]: "The latter ('direct' effects) are responsible for the positive inotropic effect of digitalis."

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GLYCOLYSIS AND ELECTROGENESIS

In his recent review Opie[1] has attempted to transfer some experimental results to medical practice. We think, however, that the review should have put major emphasis on the already proved role of anaerobic glycolysis in cardiac electrogenesis. Opie[1] mentions the problem only briefly when he describes the effect of free fatty acids on the action potential of ischemic myocardium.

Prasad and MacLeod,[2] and McDonald and MacLeod[3] have shown the following in the guinea pig anoxic ventricular myocardium: (1) To keep cardiac action potential amplitude and duration equal to the control value, an increase of medium glucose concentration is sufficient; in contrast, glycolytic adenosine triphosphate (ATP) is unable to preserve the contractile activity; (2) cardiac action potential amplitude and duration depend on the slow inward current, and this current can be influenced by metabolism; (3) action potential amplitude is related to the metabolic state of the muscle, but not to the intracellular sodium ion; (4) the resting potential is influenced not only by E_k but also by an electrogenic sodium pump that is in turn dependent on glycolytic adenosine triphosphate.

Similar results have been obtained using the isolated perfused heart.[4] On the basis of these experiments it has been pointed out that (1) total myocardial ATP content is not related to electrographic changes of the initial phase of ischemia or anoxia; (2) insulin and glucose prevent electrographic changes and the onset of arrhythmias during anoxic perfusion; (3) inhibition of glycolysis by 2-deoxyglucose or iodoacetic acid provokes changes in the S-T segment and T wave and initiates

arrhythmias and ventricular fibrillation even in the oxygenated perfused heart.

We think it necessary to add the following to Opie's seven hypothetical mechanisms for the therapeutic effect of glucose-insulin-potassium solutions: infusion of glucose-insulin-potassium may normalize the electric activity of ischemic cells by activating glycolysis.

At the periphery of the infarct are some damaged cells that survive. These cells may form an electrically unstable focus responsible for the onset of arrhythmias during the acute myocardial infarction.[5] If glucose-insulin-potassium solutions are really efficient during acute infarction, we think that the mechanism of action is probably related to normalization of the action potential of ischemic cells. It has not been clearly shown that glycolytic ATP is able to sustain the physiologic structure of a working heart,[6] but it is certainly a good fuel for the electric activity of the heart that has a very low energy requirement.[7] After the first minute of ischemia a decrease in anaerobic energy production occurs owing to an increase in intracellular hydrogen ion and subsequent inhibition of glycolysis.[8]

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REPLY

The hypothesis that glycolysis could be related to electrogenesis merits careful consideration in explaining the effects of glucose and of fatty acids on the infarcting myocardium. More specifically, the adenosine triphosphate (ATP) concentration in or near the plasma membrane may play a role in the promotion of the slow inward calcium current associated with the plateau of the action potential[1] (Fig. 1). Such ATP is thought to exist in a compartment not exchanging readily with mitochondrially produced ATP, but rather to be generated by glycolysis.[2] The rates of glycolytically generated ATP in the normally oxygenated heart are negligible from the point of view of the overall energy requirements of the heart, but this hypothesis would nevertheless accord a special role to such glycolytic ATP. The hypothesis was referred to in my review, but could not be discussed in depth because of limited space.

In a truly anoxic cell, ATP can be made only by anaerobic production of lactate except for very exceptional circumstances in which mitochondrial electron flow can be reversed.[3] In the experiments of Prasad and MacLeod,[4] anoxic papillary muscle was used and the rate of lactate production correlated

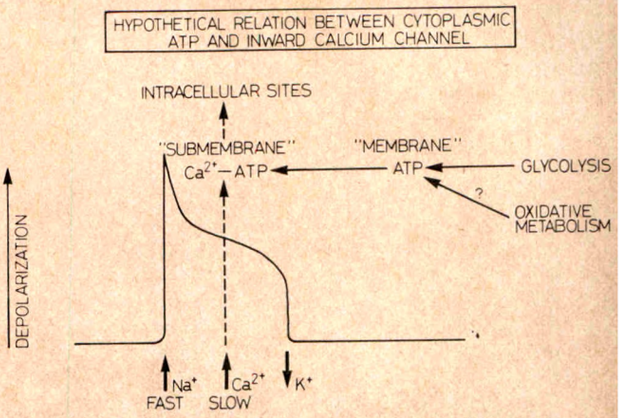

FIGURE 1. The hypothetical relation between cytoplasmic ATP and the inward calcium channel is shown schematically. Girardier and co-workers[1,2,6] postulate that submembrane Ca^{2+}-ATP complexes may help remove Ca^{2+} that has entered through the slow inward Ca^{2+} current to more distant intracellular sites. ATP available for "membrane" functions such as the action potential is thought to be generated by glycolysis, but evidence suggests that oxidative metabolism can equally well provide such ATP.

with the duration of the action potential. But in the well oxygenated muscle by far the major part of ATP is made in the mitochondria and then transported to the cytoplasm (Fig. 1 of my article). Some data of Prasad and MacLeod[4] suggest that, in the adult heart, mitochondrially produced ATP enters the same compartment as glycolytically produced ATP to maintain the action potential. To establish whether mitochondrially produced ATP could maintain the action potential, Girardier and I compared the action potential obtained by a floating microelectrode from the isolated perfused rat heart when it was perfused with pyruvate with values obtained during glucose perfusion (unpublished data); there were essentially no major differences except that the conduction velocity and heart rate were accelerated by pyruvate. No arrhythmias developed. In the presence of pyruvate, glycolytic flux from glycogen was totally inhibited and thus the production of glycolytic ATP was severely limited. Thus normal electrical activity of the oxygenated perfused heart could be maintained in the absence of glycolytic flux. However, in whole heart underperfusion causing ischemia, glucose inhibited and pyruvate promoted the incidence of reperfusion arrhythmias and enzyme release, and the difference could be related to the rate of anaerobic ATP production during the ischemic period.[5] The earlier experiments of Cheneval et al.[6] used fetal cultured cells, which generally are more dependent on glycolytic metabolism than is the adult heart; thus the results may not be directly extrapolated to the different metabolic pattern in the adult heart.

The perfused heart experiments described by Carbonin are of interest but his original data have not been passed on to me and a detailed commentary would be inappropriate. If the isolated hearts were perfused with glucose as the only substrate, then deoxyglucose could have deprived the heart of all exogenous substrate. Development of arrhythmias and ventricular fibrillation during substrate depletion was described in 1958[7] but does not necessarily prove a relation between glycolytic ATP and electrical events because pyruvate could also arrest fibrillation induced by lack of glucose. Potassium loss may be an important factor.[8] Experiments with omission of glucose as external substrate must distinguish between effects specific to the absence of glucose uptake, and nonspecific effects of substrate deprivation, which can shorten the effective refractory period.[9]

Carbonin suggests that, at the edge of the infarct, there are cells that are deficient in ATP and that glucose-insulin-potassium (GIK) could act on such cells. In cells severely damaged by ischemia, inhibition of anaerobic energy production by accumulation of protons and lactate suggests that not much increase in anaerobic glycolysis is going to occur as a result of glucose-insulin-potassium therapy. Administration of glucose-insulin-potassium increases glycolytic flux in the peri-infarct border zone in the baboon[10] and probably also in the peripheral infarct zone of developing dog infarcts,[11] which allows for the possible existence of the mechanism suggested by Carbonin.

In the infarcting animal myocardium the collateral blood flow ensures that the predominant metabolism of the infarcting zone (*taken as a whole*) is still oxidative, and this conclusion also applies to the periphery of the infarct.[12] Aerobic glycolysis would be increased if glucose-insulin-potassium caused increased glucose uptake in the peripheral infarct zone as calculations suggest.[11] Thus it may be valid to distinguish between aerobic and anaerobic glycolysis in considering the effects of glucose-insulin-potassium. Whereas glucose-insulin-potassium may increase aerobic glycolysis (that is, glycolytic flux with oxidative metabolism of pyruvate as its end product), it probably does not greatly increase anaerobic glycolysis (with lactate as end product). Although the rates calculated for production of glycolytic ATP are not consistently lowered when infarction is developing,[12] the methods used for calculation yield only approximate data. Increased aerobic glycolysis during glucose-insulin-potassium therapy would imply increased generation of glycolytic cytoplasmic ATP. It is easier to quantify production of glycolytic ATP in the ischemia-reperfusion rat heart model in which there is increased glycolytic ATP production in ischemic hearts perfused with glucose by comparison with pyruvate or acetate, but such underperfusion is a model of mild ischemia; whether it corresponds to any groups of cells in developing infarction remains to be established.

The possible role of glucose-insulin-potassium and glycolytic cytoplasmic ATP in the maintenance of action potential is an important subject that requires further work to clarify the relation.

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EFFICACY OF LONG-ACTING NITRATES
I. Sublingual Versus Oral Administration

In their recent editorial, Krantz and Leake[1] took issue with our thesis that orally administered organic nitrates are rapidly and efficiently degraded by the liver and therefore cannot exert a clinically useful effect since essentially none of the parent compound is in the circulation. Because a large number of patients with angina pectoris still receive these agents for long-term prophylactic therapy, a review of some recent evidence is pertinent.

The major premise of our investigations is that intact unmetabolized organic nitrate is the pharmacologically active form that accounts for the action of this class of agents.[2] Blood clearance data indicate that intravenous administration of the parent nitrate ester (including the so-called long-acting nitrates) to experimental animals has transient circulating lifetime (only 2 to 5 minutes) whereas the nitrate metabolites circulate for hours.[3,4] However, the duration of the vasodilator effectiveness of organic nitrates in experimental animals is in direct temporal correlation with blood levels of the intact ester but is completely out of phase with circulating metabolite levels. The enzyme responsible for this efficient destruction of organic nitrates occurs in man as well as in experimental animals.[4]

Pentaerythritol tetranitrate and pentaerythritol trinitrate have been advocated for oral use and are suggested to produce a prolonged effect in man and experimental animals.[5,6] Analysis of the blood of 15 human volunteers treated (orally) with radioactive pentaerythritol tetranitrate indicated that no intact pentaerythritol tetranitrate or pentaerythritol trinitrate could be detected in the plasma at any time after drug administration. The major circulating form of the drug was pentaerythritol with lower levels of pentaerythritol mononitrate and trace amounts of pentaerythritol dinitrate.[7–9] The prolonged hypotension produced by pentaerythritol trinitrate in man was explained by the persisting levels of pentaerythritol di- and mononitrate metabolites in plasma.[10] In a recent investigation (including the manufacturers' scientists) several important observations were demonstrated[11]: (1) The duration of the coronary vasodilation and peripheral hypotension in dogs after intravenous injection of pentaerythritol trinitrate was the same (about 2 minutes) as after administration of the short-acting nitroglycerin even though pentaerythritol trinitrate is advocated as a "long acting" nitrate. (2) Pentaerythritol trinitrate was only 20 percent as potent as nitroglycerin in dogs as a coronary vasodilator and as a systemic vasodepressor. Pentaerythritol dinitrate had 1 percent of the potency, and the major circulating form of the drug, pentaerythritol, was completely inactive. (3) There was cross tolerance between nitroglycerin and pentaerythritol trinitrate and also between pentaerythritol trinitrate and its much less active metabolites. The authors concluded that "these metabolites are without significant vasodilator activity in comparison to the parent compound; therefore their persistent plasma level cannot be responsible for the sustained action of pentaerythritol trinitrate in man."[11]

The other clinically employed organic nitrate that has been extensively studied is isosorbide dinitrate. After intravenous administration to dogs, isosorbide dinitrate was also rapidly cleared from the blood (half-time 5 minutes).[3,12,13] The major plasma metabolite was 5-isosorbide-mononitrate (65 percent of the administered dose).[12] Comparable data were obtained after oral administration of radioactive isosorbide dinitrate to human volunteers.[14] The radioactivity in blood was primarily 5-isosorbide mononitrate with little unchanged isosorbide-dinitrate present; thus the authors suggest that the metabolites account for the pharmacologic action. This conclusion is not supported by the biologic activity of the metabolites. Whereas intact isosorbide dinitrate has only 3.5 percent the potency of nitroglycerin as a coronary vasodilator and a vasodepressor, the major circulating metabolite, 5-isosorbide mononitrate, had only 1 to 3 percent of the potency of isosorbide dinitrate.[15,16]

The foregoing evidence does not suggest the existence of an active intact parent nitrate in the circulation after oral administration. Why, then, do some clinicians and experimental workers advocate the oral use of organic nitrates as long-acting prophylactic antianginal medication? It is difficult to perform an adequate clinical trial for an antianginal agent. The design of many previously performed clinical studies prejudiced the results. Stipe and Fink[17] extensively reviewed the literature from 1952 to 1972 on the efficacy of organic nitrates as prophylactic therapy for angina pectoris. They found 36 clinical studies on long-term prophylaxis with organic nitrates. When no precautions about experimental design were taken, 50 percent of the patients reported the nitrates to be effective. However, in clinical studies that included controls, double-blinding, randomization, placebo, crossover and statistical analysis, fewer than 10 percent of patients with angina concluded that organic nitrates were efficacious. According to Modell,[18] "The history of failure with so-called long-acting nitrates is an unbroken one."

It should be recalled that the Food and Drug Administration classified organic nitrates in the "possibly" effective category, which by their definition means no proof of efficacy. Indeed, it seems strange that patients taking "long-acting" nitrates still use nitroglycerin for acute attacks when in fact these agents appear to have the same mechanism of action.[11] One temptation that could arise is that clinicians would administer much larger doses of organic nitrate in the hope of exceeding the hepatic degradation capacity. Such an approach would be expected, unfortunately, to exaggerate side effects of and to induce tolerance to the administered agent and cross tolerance to nitroglycerin.[11,19]

Finally, it should be emphasized that sublingual administration, which initially avoids hepatic destruction of organic nitrates, still represents a rational approach to the acute relief of an attack of angina pectoris.

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REPLY

We agree with Needleman that "the intact, unmetabolized organic nitrate is the pharmacologically active form that accounts for the major action of this class of drugs." Indeed, one of us[1] established this a third of a century ago. What we cannot understand is his suggestion that these agents lack activity upon oral administration.

We do not agree that "the duration of the vasodilator effectiveness of organic nitrates in experimental animals is in direct temporal correlation with blood levels of the intact ester." We contend that the portion of the dose of the intact molecule that escapes degradation in the liver elicits its effect in the receptor sites of the organs involved with the response to the drug. To repeat what we previously demonstrated several years ago, using the perfused rabbit's heart and nitroglycerin: The coronary vessels were dilated to produce a 50 percent increased flow, but only 14 percent of the drug was fixed in the receptor sites[2]; as a first approximation on a molecular basis the heart retained 2×10^{17} molecules of nitroglycerin. When one thinks in these terms it is not difficult to perceive how so little can do so much. Our concept is in accord with that of Goldstein[3] of the National Heart and Lung Institute, who has stated, "Vasodilator activity might not depend on the drugs' prolonged presence in the bloodstream, but on their rapid incorporation into the cells lining the blood vessels." We believe that this concept has been overlooked by Dr. Needleman and acceptance of it would clarify the disagreement between his experiments, the current work of others and the century of work before his advent in the field. This concept would also explain the therapeutic value of delayed release nitroglycerin tablets.

Needleman states that isosorbide dinitrate is only 3.5 percent as potent as nitroglycerin. We disagree. The effective dose of nitroglycerin is 0.65 mg and that of isosorbide dinitrate is 5 mg; thus the correct ratio is $0.65/5 \times 100 = 13$ percent. In contrast with the findings of Needleman, Franciosa et al.[4] found that isosorbide dinitrate given orally was "an effective vasodilator in patients with heart failure" and Wendt[5] noted that "both the 2- and 5- mononitrate esters of isosorbide produce hemodynamic effects qualitatively similar to those observed after isosorbide dinitrate."

With regard to pentaerythritol tetranitrate, Needleman fails to achieve his stated objective of reviewing recent evidence. He neglects the report that pentaerythritol tetranitrate has a half-life of 2 hours in the rat.[6] Further, he has ignored the fact that pentaerythritol is a prodrug and that its metabolite pentaerythritol trinitrate is an active molecular species although he cites studies that demonstrated the activity of this metabolite in animals (his reference 11), and one study mentions activity in man.[7]

We strongly urge Needleman to ingest 5 to 10 mg of isosorbide dinitrate to see what effect it has upon his blood pressure. After this we suggest he follow the same procedure with 20 mg of Peritrate.

We agree with Needleman that it is difficult to evaluate drug efficacy in coronary insufficiency. However, in a carefully controlled (three phase experimental design) study of 53 patients Winsor and Berger[8] used orally administered sustained release nitroglycerin tablets (Nitrong®) and found that 47.2 percent of the patients had fewer and less severe anginal attacks.

We also agree that sublingual administration is the most satisfactory method of giving the long- and short-acting organic nitrates. However, we cannot agree that they are without effect when given orally. This statement is a contradiction to an avalanche of data from current clinical studies and those of the past 100 years.

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EFFICACY OF LONG-ACTING NITRATES
II. Peroral Isosorbide Dinitrate

With reference to the recent editorial of Krantz and Leake, Shane[1] recently studied plasma concentrations of isosorbide dinitrate by the gas/liquid chromatography-method of Rosseel and Bogaert[2] and found that isosorbide dinitrate is "more effective when administered orally and in larger doses than are conventional." Stauch et al.[3] recently demonstrated with effort tests the activity of 2- and 5-isosorbide mononitrates in patients with proved coronary heart disease and confirmed the previous experimental findings of Bogaert and Rosseel.[4] Needleman himself[5] did not exclude the possibility that these metabolites were the basis for the sustained action of long-acting nitrates. The problem of quantity (plasma concentrations) should not be overestimated: Even the earlier studies[6] do not suggest a relation between plasma levels and effects of the drug.

Animal experimental results should be reevaluated from this new point of view, especially since many experimental and clinical studies in man demonstrate with objective measures the efficacy of long-acting nitrates. Franciosa et al.[7] compared, in a double-blind study, orally administered isosorbide dinitrate with placebo and found a significant reduction of left ventricular filling pressure persisting for 4 to 5 hours. Wolf et al.[8] administered the same dose (20 mg) of isosorbide dinitrate and demonstrated a significant reduction in mean arterial, pulmonary arterial and pulmonary capillary pressure during the first hour after ingestion. Cardiac output and left ventricular work decreased correspondingly for up to 4 hours. The same results were obtained by Bussmann et al.[9] in patients with acute myocardial infarction. Similar results were obtained after oral administration of 5 mg, in patients with cor pulmonale[10] and coronary heart disease[11] and, after oral administration of 10 mg, in a double-blind comparison with placebo.[12] These data were reported in 1975. Probably the first double-blind clinical trial in man (comparative study) showing the peroral activity of sorbide dinitrate was performed in 1947 by Goldberg[13] in hypertensive patients: The average duration of the significant antihypertensive effect was 4.2 hours (range 1 to 24 hours). Additional proof of the therapeutic value of isosorbide dinitrate is found in comparative component studies,[14–16] in which isosorbide dinitrate is combined with beta blocking agents.[14] These studies use measurable variables and demonstrate not only the superiority of the combination of agents but also the efficacy of isosorbide dinitrate.

These studies show that the belief of clinicians in the activity of isosorbide dinitrate (and other long-acting nitrates) has a scientific foundation. We should not overestimate the value of pharmacologic experiments in animals and should correct some ideas of the last 3 to 4 years because we believe with Needleman[17] that "science and medicine should be self-correcting institutions."

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LATE SUPERNORMAL EXCITATION

Igarashi and Ayabe discuss a "late" supernormal phase of ventricular excitability, attributing it to summation, in some cases because of ". . . electrotonic spread of atrial depolarization potentials." I would like to make two comments.

Beat to beat threshold variation is very common when using transvenous temporary pacing leads, as in their study. Respiratory variation alone frequently can cause threshold changes of the magnitude reported in the "supernormal phase." Without a demonstrably fixed stable electrode system, small beat to beat changes in catheter electrode position can account for threshold changes.

Atrial depolarization has previously been noted to alter threshold,[2] with intervals of elevation and reduction of threshold following the P wave. As correctly pointed out to me in review of an unpublished paper, atrial mechanical contraction may have an effect on electrode position, and one need not invoke the more abstruse concepts, such as Wedensky facilitation, to explain the phenomenon. Following that lead, I then made cine films of eight implanted (long-term) pacing catheters, showing distinct movement of the tip of the catheter after atrial contraction. In some instances atrial contraction moved the catheter tip farther into the right ventricular apex (presumably making better contact and lowering threshold), and in other cases atrial contraction caused buckling of the catheter and some retraction of the catheter tip (opposite effect). Movement of temporary pacing catheters is frequently more marked.

Although one cannot disprove summation of subthreshold stimuli, the mechanical factors would have to be controlled to support such a hypothesis.

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2. **Preston TA:** Atrial phasic inhibitation of implanted cardiac pacemakers. Circulation 30:Suppl VI:VI-158, 1968

REPLY

Mechanical influence of atrial contraction on ventricular wall motion is documented and can be observed in an echocardiogram. Unless epicardial electrodes are used, such influences of ventricular wall motion on endocardial electrode position can hardly be denied.

We have not had a chance to use epicardial electrodes for the study of "late supernormal excitation" in man. However, in a study from our laboratory (our original Ref. 14), Arbel and others pertinently showed the presence of "late supernormal excitation" in dogs using epicardial stimulation. In their study they found hardly any mechanical influence on the electrode position as a result of atrial contraction. Thus, our conclusion with regard to the (electrical) contribution of atrial depolarization on ventricular excitability in late diastole can be verified.

Masao Igarashi, MD
Takao Ayabe, MD
St. Luke's International Hospital
Tokyo, Japan

Fee Change: Sub-Board of Pediatric Cardiology

Due to the rising costs in the administration of the written and oral examinations of the Sub-Board of Pediatric Cardiology, the fee for examination has been increased to $450.00 ($150.00 registration and $300.00 examination fees). This is effective immediately; therefore, candidates who wish to apply for the July 22, 1977 written and November 3–4, 1977 oral examinations of the Sub-Board must submit the $450.00 fee with their application. Registration extends from August 1, 1976 to November 30, 1976. Application materials are available from the American Board of Pediatrics, Children's Hospital, 34th St. & Civic Center Blvd., Philadelphia, PA 19104

Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

To be arranged individually **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

SEPT. 8–10 **Venous Thrombosis Pulmonary Embolus Complex.** Orville Horwitz, FACC and Frank D. Gray, directors and Henry Berkowitz, H. James Day and L. Henry Edmunds, FACC, co-directors. The Hilton Hotel of Philadelphia, Philadelphia, Pa.

SEPT. 13–14 **Exercise Testing in Children and Young Adults.** Frederick W. James and Samuel Kaplan, FACC, directors. Children's Hospital Medical Center, Cincinnati, Ohio

SEPT. 13–17 **Cardiology for the Consultant.** E. Grey Dimond, FACC, James E. Crockett, FACC and Don R. Santschi, FACC, directors. University of Missouri-Kansas City School of Medicine, Kansas City, Mo.

SEPT. 23–25 **The Clinical Spectrum of Adult Heart Disease.** Jonathan Abrams, FACC, director and Paul T. Cochran, FACC, co-director. Basic Medical Sciences Building of University of New Mexico Health Sciences Center, Albuquerque, N. Mex.

SEPT. 28–30 **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya, James C. Dillon, FACC and Arthur E. Weyman, co-directors.

OCT. 11–13 **Electrocardiography: Core Curriculum and Self-Assessment.** Leonard S. Dreifus, FACC, director. University City Holiday Inn, Philadelphia, Pa.

OCT. 11–13 **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC and Borys Surawicz, FACC, directors. Indiana University Medical Center, Indianapolis, Ind.

OCT. 11–13 **Electrocardiography: Core Curriculum and Self-Assessment.** Alberto Benchimol, FACC, director. Safari Resort Hotel, Scottsdale, Ariz.

OCT. 12–14 **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Golden Gateway Holiday Inn, San Francisco, Calif.

OCT. 19–21 **Ischemic Heart Disease: Current Concepts.** William J. Grace, FACC, James T. Mazzara, FACC and Richard J. Kennedy, FACC, directors. St. Vincent's Hospital and Medical Center of New York, New York, N.Y.

OCT. 21–23 **New Techniques and Concepts in Cardiology: Exercise Stress, Exercise Testing and Cardiac Rehabilitation.** Stephen E. Epstein, FACC, director. The Washington Hilton Hotel, Washington, D.C.

NEW MEMBERS

The following individuals were elected to membership in the American College of Cardiology on July 8, 1976, in the category indicated.

FELLOWSHIP

ALAN, Richard J., MD, California
ALEXANDRIDES, Kosmas, MD, Greece
ALFARO A., Federico G., MD, Guatemala
ALLEN, Hugh D., MD, Arizona
AMAT-Y-LEON, Fernando, MD, Illinois
ATKINS, James M., MD, Texas
AUSTIN, Stephen M., MD, Maryland
BATCHELDER, John E., MD, Indiana
BEDARD, J. Pierre, MD, Canada
BEMIS, Charles E., MD, Pennsylvania
BERKE, David K., MD, California
BERNDT, Theodore R., MD, Louisiana
BESCH, Henry R., Jr., PhD, Indiana
BRADY, Alfred B., MD, Texas
BURG, John R., MD, Montana
CHAITMAN, Bernard R., MD, Canada
CHAVEZ-RIVERA, Ignacio, MD, Mexico

CO, Eddy D., MD, Wisconsin
COHN, Herbert E., MD, Massachusetts
COOK, Robinson, MD, Idaho
COOPER, Gary R., MD, Florida
COPEN, David L., MD, Connecticut
CRAWFORD, Michael H., MD, California
DEGNAN, Walter C., MD, Montana
DePASQUALE, Nicholas P., MD, New York
DEUTSCH Paul G., MD, New York
DOWNING, S. Evans, MD, Connecticut
DUNKMAN, W. Bruce, MD, Pennsylvania
FAHMY, Abdel-Rahman, MD, Saudi Arabia
FARAH, Michel G., MD, Ohio
FERGUSON, Earl W., MD, Texas
FERLINZ, Jack, MD, California
FISHER, Michael L., MD, Maryland
FRANK, Stuart, MD, California
FREDERIKSEN, Rand T., MD, Tennessee
GALST, Gerald, MD, New York
GENTZLER, Richard D., II, MD, Texas
GEORGIEV, Maria T., MD, West Virginia
GIMBEL, Kenneth S., MD, Maryland
GOTTLIEB, Ronald S., MD, Pennsylvania
GUPTA, Parkash D., MD, Illinois
HAMID, Imtiaz, MD, Illinois
HAYES, Arthur H., Jr., MD, Pennsylvania
HERMANN, Heinz J., MD, Texas
HIGASHINO, Stanley M., MD, California
JOSEPHSON, Mark E., MD, Pennsylvania
KAJIWARA, Nagao, MD, Japan
KATTUS, Albert A., MD, California
KELLY, David T., MD, Maryland
KENDALL, Malcolm E., MD, Illinois
KEON, Wilbert J., MD, Canada
KHAN, Abdul H., MD, Pakistan
KINCAID, Daniel T., MD, Wisconsin
KIRKPATRICK, Stanley E., MD, California
KLIE, Jack H., MD, Rhode Island
KRAMER, John D., MD, Ohio
LAZIK, Arthur J., MD, California
LEFER, Allan M., PhD, Pennsylvania
LEVIN, Daniel L., MD, Texas
LEVITAN, Benjamin, MD, Canada
McGAFF, Charles J., MD, Ohio
MARCUS, Gary B., MD, California
MARIN-GARCIA, Jose, MD, Pennsylvania
MARTIN, Richard H., MD, Missouri
MELENDEZ, Libardo J., MD, Canada
MORARAS, Theeragul, MD, Illinois
MUHAMMAD, Ali, MB, Pakistan
NABI, Nasser, MD, Massachusetts
NATHAN, David, MB, Canada
PEARLE, David L., MD, District of Columbia
PERLROTH, Mark G., MD, California
POSNER, Christian J., MD, California
PROPERT, David B., MD, Virginia
RAPAPORT, Elliot, MD, California
RASKOFF, William J., MD, California
RAY, C. Thorpe, MD, Louisiana
RECHNITZER, Peter A., MD, Canada
REID, Philip R., MD, Maryland
ROGERS, William J., MD, Alabama
ROSIN, Elaine Y., MD, Ohio
ROSSEN, Ronald M., MD, California
RUSSELL, Thomas, II, MD, Minnesota
SAHN, David J., MD, Arizona
SALEM, Deeb N., MD, Massachusetts
SALTUPS, Andris, MD, Australia
SAYEED, Majeed A., MD, New York
SCHWARTZ, Kenneth V., MD, Connecticut
SHETTIGAR, Udipi R., MD, California
SHORT, Floyd A., MD, Washington
SIEGEL, Fredric A., MD, District of Columbia
SILVERMAN, Norman H., MD, California
SORENSEN, Herman D., MD, Montana
STONE, John M., MD, Michigan
SULLIVAN, Thomas E., MD, Massachusetts
TERRY, Richard W., MD, California
THOMAS, J. R., MD, Tennessee
TUCKER, Herbert D., MD, Louisiana
VARGHESE, P. Jacob, MD, Maryland
WALTER, Paul F., MD, Georgia
WARREN, Stafford G., MD, West Virginia
WEISS, Edward S., MD, Missouri
WELD, Francis M., MD, New York
WILSON, Charles L., MD, Texas
WRAY, Taylor M., MD, Tennessee
WU, Delon, MB, Illinois
ZWERLING, Leonard J., MD, Massachusetts

The following individuals were elected to membership in the American College of Cardiology on February 22, 1976, in the category indicated.

FELLOWSHIP

GOLDBERG, Leonard M., MD, Oregon
KAZI, Majid-Uddin, MD, Saudi-Arabia
LUIKART, William M., MD, Louisiana
ZALIS, Edwin G., MD, California

26th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY

Philadelphia, Pennsylvania **February 28–March 3, 1977**

- **Abstracts**
  Entries must be postmarked no later than September 20, 1976
- **Technical Exhibits**
  Deadline for requests for space: October 15, 1976
- **Scientific Exhibits**
  Deadline for requests for space: October 15, 1976
- **Young Investigators' Awards Competition**
  Entries must be postmarked no later than November 1, 1976

For application forms, write Patrick A. Ziarnik, Director, Annual Scientific Session Department, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

AMERICAN COLLEGE OF CARDIOLOGY

Young Investigators' Awards for 1977

First Award:	$1000
Honorable Mention:	$250
Three Additional Awards:	$100 each

Conditions for participation in the competition:

ELIGIBILITY Any physician/scientist who is presently in a residency or fellowship training program or who has been in such a program within the past three years is eligible to submit a paper in the competition. A senior medical student who will have received his M.D. degree by the time of the competition is eligible. A student in one of the basic sciences working in a problem intimately connected with cardiology who will have received a Ph.D. degree by the time of the competition is also eligible.

SCOPE Competitive presentations of papers will be given at the 26th Annual Scientific Session of the American College of Cardiology, February 28–March 3, 1977 in Philadelphia, Pennsylvania. A formal presentation, 12 minutes in length, describing original investigation in which the entrant either did the work or was a significant member of the investigating team, is required of each entrant.

PROCEDURE

1. An original and three (3) copies of an abstract of the paper are required. The abstract must be submitted typed single-spaced on special YIA Abstract Reproduction Forms. If it is selected for presentation, the form will then be used as the master copy for printing by photo-offset in the Abstracts Publication which will be distributed at the time of the Annual Scientific Session.
2. An original manuscript, typed double-spaced, is required.
3. Include a letter or certification form indicating your intention to enter the competition, and an accompanying letter or verification form from your Chief of Service or Laboratory indicating his willingness to have the material entered in the competition.
4. Complete and return the 3″ × 5″ ivory index card containing:
   a. Entrant and his address
   b. Co-author(s)
   c. Title of paper
   d. Institution(s), City and State
5. Forward to: Patrick A. Ziarnik, Director, Annual Scientific Session Department, American College of Cardiology, 9650 Rockville Pike, Bethesda, Maryland 20014.

DEADLINE NOVEMBER 1, 1976

OPTION If you wish to have your paper considered for presentation at one of the abstract sessions in addition to the YIA competition, your abstract must be submitted by September 20, 1976.

PLEASE NOTE Special abstract reproduction forms, certification and verification forms and rules for submitting abstracts are supplied on request to the College at the address above. These "special" forms are to be used by each entrant.

Support for the awards is provided as a Professional Education Grant of Searle Laboratories, a Division of G. D. Searle & Company.

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[1]Little, Arthur D. Inc. A review of the Patient Monitoring System at the University of Alabama Medical Center; prepared for National Center for Health Services Research and Development, March 1973.

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Practical Considerations

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While every MI patient is not a candidate for oral anticoagulation therapy, a history of previous infarct or angina, persistent atrial fibrillation or congestive failure, severe hypotension or shock or serious arrhythmia may increase risk of thromboembolic complications.

In addition, certain procedures often place your surgical patient, particularly if he's over 40 years of age, in the high risk category—cup arthroplasty or pelvic surgery, heart valve replacement, reparative vascular surgery.

Your geriatric patient, too, is at high risk of thromboembolism if he's suffered a fracture—especially of the hip, pelvis or a lower extremity—or if his history includes venous insufficiency.

For any of these individuals, obesity, previous episodes of venous thrombosis or pulmonary embolism and a future including prolonged bed rest all increase the risk of thromboembolic complications, and make him a candidate for oral anticoagulation.

Laboratory monitoring

For every patient receiving COUMADIN® (*crystalline* sodium warfarin), frequent laboratory monitoring is a key to effective therapy. Determine prothrombin time daily until results stabilize in the therapeutic range —1½ to 2½ times normal. Individualize dosage and administration as indicated by prothrombin time results. Determine subsequent prothrombin times periodically throughout the course of therapy.

Educating your patient

Because a patient is generally more reliable if he understands his condition and his medication, he should be made aware of the factors that may influence his prothrombin time and, therefore, his response to COUMADIN®—dietary change, travel, other medication, change in physical condition and abrupt environmental change. What's more, he should know the importance of regularly taking the exact dosage of COUMADIN® prescribed and of keeping every appointment with you and with the laboratory.

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Therapeutic principles put into practice

COUMADIN®
(CRYSTALLINE SODIUM WARFARIN*)

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN* is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional and lumbar block anesthesia.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN* are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Pregnancy–COUMADIN* passes through the placental barrier, and the danger of hemorrhage to the fetus exists even to the point of fatal hemorrhage **in utero,** even in the accepted therapeutic range of maternal prothrombin level. Close observation and laboratory control are essential. The newborn may be particularly sensitive to sodium warfarin. There have been reports of birth malformations in children born to mothers who have been treated with warfarin during the first trimester of pregnancy. Whether warfarin was in fact the responsible agent has not been established. Therefore, women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed. If COUMADIN* must be used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks. **Lactation**–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Spinal puncture. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN*, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN*.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN* overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methylphenidate; monoamine oxidase inhibitors; nalidixic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates (in excess of 1 Gm/day); sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamine hydrate†; chlordiazepoxide; cholestyramine; COUMADIN* underdosage; diet high i fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperi contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time deter

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which r decrease his sensitivity to COUMADIN*. Because the net effect on his prothrombin unpredictable under these circumstances, more frequent laboratory monitoring is ad

Drugs not yet shown to interact or not to interact with coumarins are best regard when their administration is started or stopped, the prothrombin time should be than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropa and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the ference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN* (crystalline sodium wa

1. Minor or major hemorrhage from any tissue or organ–which is an extension of th prothrombinopenia. The signs and symptoms will vary according to the location and bleeding. Therefore the possibility of hemorrhage should be considered in evaluati anticoagulated patient with complaints which do not indicate an obvious diagr anticoagulant therapy does not always correlate with prothrombin activity. (See T DOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic ran investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulce

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urti nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersen extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to imp clotting mechanism to such an extent that thrombosis will not occur, but at the sa extensive impairment as might produce spontaneous bleeding. Effective therapeu complications can best be achieved in cooperative and well-instructed patients, informed of their status between visits. COUMADIN* patient aids are available to phy

The administration and dosage of COUMADIN* must be individualized for each p particular patient's sensitivity to the drug as indicated by the prothrombin time. reflects the depression of vitamin K-dependent factors, namely Factors VII, IX, X an by coumarin anticoagulants. There are several modifications of the Quick one-stage the physician should become familiar with the specific method used in his laboratory

Administration of COUMADIN* should be gauged according to prothrombin time d able method. The blood prothrombin time should usually be determined daily after t initial dose until prothrombin time results stabilize in the therapeutic range. Interva prothrombin time determinations should be based upon the physician's judgment o and response to warfarin in order to maintain the individual within the therapeutic vals for prothrombin time determinations have usually fallen within the range of o factory levels for maintenance of therapeutic prothrombinopenia are 1½ to prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitate only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg da is provided by breaking scored tablets in half. The individual dose and interval sh patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individu coagulant therapy should be continued until the danger of thrombosis and embolism

Treatment during dentistry and surgery–The management of patients who unde procedures requires close liaison between attending physicians, surgeons and d anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoa at full doses, some patients may hemorrhage excessively. If it is elected to adminis to, during, or immediately following dental or surgical procedures, it is recommer COUMADIN* be adjusted to maintain the prothrombin time at approximately 1½ level. The operative site should be sufficiently limited to permit the effective use of mostasis including absorbable hemostatic agents, sutures, and pressure dressin these conditions dental and surgical procedures may be performed without undue ri

COUMADIN* with Heparin–Since a delay intervenes between the administration of therapeutic prolongation of prothrombin time, it may be advisable in situations administer sodium heparin initially along with COUMADIN. The initial dose of COUMADIN may be administered together in the same syringe. It should be noted the prothrombin time; and therefore, when patients are receiving both heparin and sample for prothrombin time determination should be drawn just prior to the ne preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours afte injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without trolled by discontinuing COUMADIN* (crystalline sodium warfarin), and if necessar administration of vitamin K_1. The appearance of microscopic hematuria, excess melena, petechiae or oozing from nicks made while shaving are early manifesta binemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, problem.

If minor bleeding persists or progresses to frank bleeding, vitamin K_1 in doses of 5 parenterally. (Please note recommendations accompanying vitamin K preparations

Fresh whole blood transfusions should be considered in cases of severe bleedin states unresponsive to vitamin K_1.

Resumption of COUMADIN* administration reverses the effect of vitamin K_1, prothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN* (crystalline sodium warfarin). For oral use, s numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose b

Injection: Available as single injection units of amorphous sodium warfarin lyophi intramuscular use in a box of 6 units. 50 mg: Unit consists of 1 vial, 50 mg; s thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide, accompanied by a 2 ml Injection. 75 mg: Unit consists of 1 vial, 75 mg; sodium chloride, 15 mg; thim adjusted with sodium hydroxide, accompanied by a 3 ml ampul Sterile Water for Inj

Sterile Water for Injection contains no antimicrobial or other substance, and it is no lar injection without first having been made approximately isotonic by the addition only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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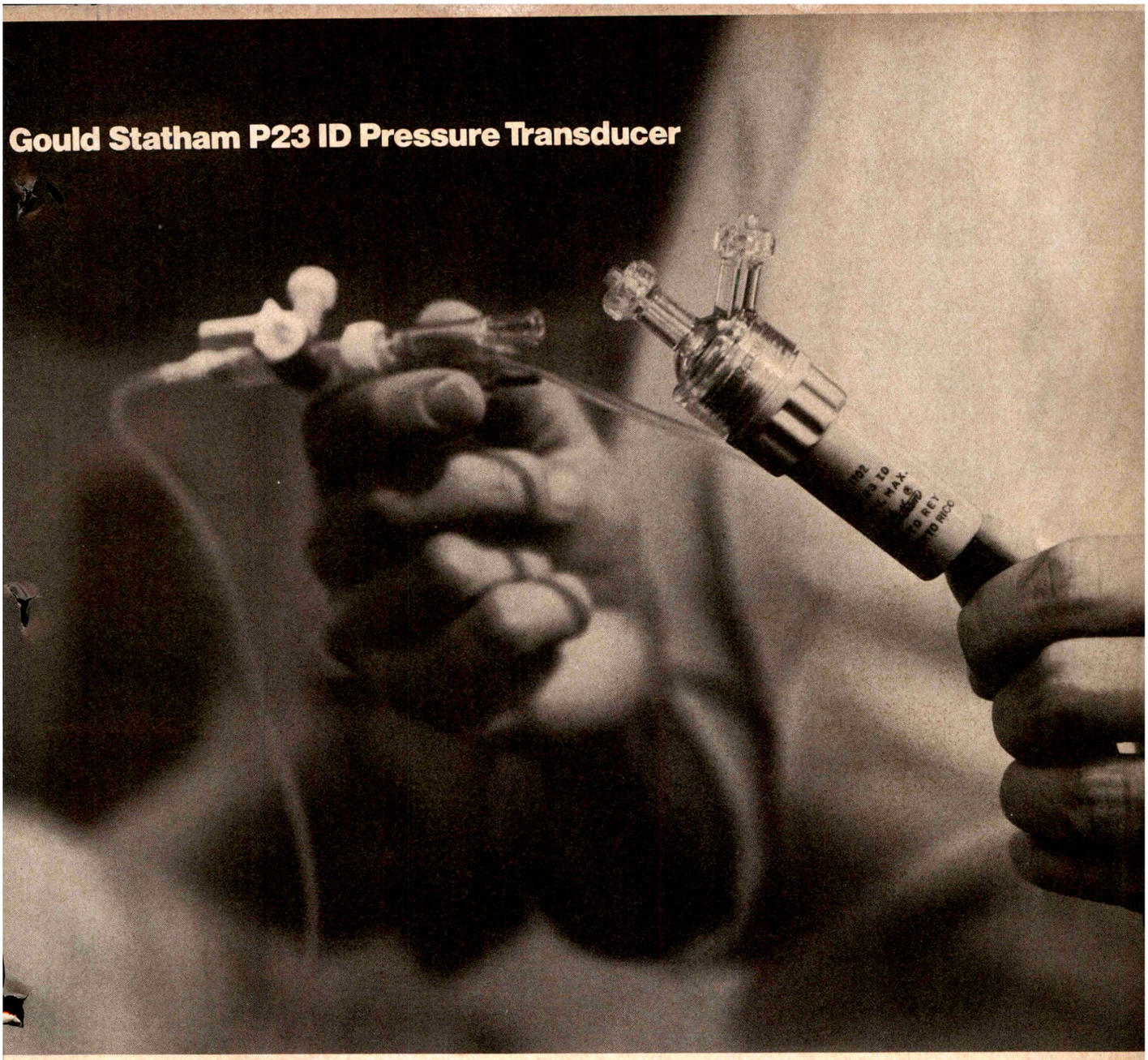

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The Gould Statham Model P23 ID Transducer is the culmination of nearly 30 years of leadership in the medical transducer field.

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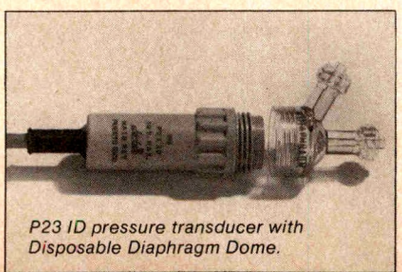
Add the Disposable Diaphragm Dome to the P23 ID or most other units in the P23 series and you have an impressive combination working for you: performance and safety with less overall cost.

For more information on the P23 ID, Disposable Diaphragm Domes, and an outstanding opportunity to upgrade your transducer inventory through a generous trade-in program, write Medical Transducer Sales Manager, Gould Inc., Statham Instruments Division, 2230 Statham Boulevard, Oxnard, CA 93030. Tel. (805) 487-8511.



P23 ID pressure transducer with Disposable Diaphragm Dome.

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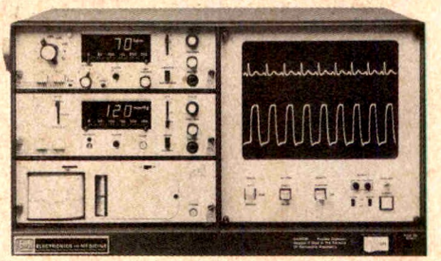

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Plus 10 years of guaranteed protection.

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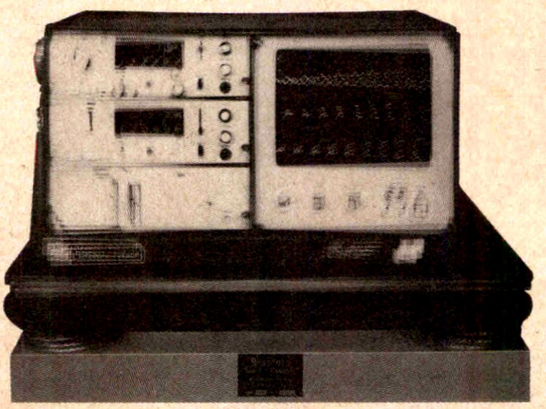

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Brief Summary **DESCRIPTION:** Nitroglycerin 2% (glyceryl trinitrate) and lactose in special lanolin-petrolatum base.
ACTION: Nitroglycerin is continuously absorbed through the skin into the circulation, thus exerting prolonged vasodilator effect.
INDICATIONS: Prevention and treatment of angina pectoris.
PRECAUTIONS: Headache is a sign of overdosage, so reduce dosage. Occasionally elderly patients may develop postural hypotension with faintness upon suddenly arising. May be contraindicated in patients with marked anemia, increased intraocular pressure or increased intracranial pressure. Don't use in patients with a known idiosyncrasy to nitrites.
DOSAGE AND ADMINISTRATION: Usual dose is 1-2 inches, as squeezed from tube. Some patients require 4-5 inches. To determine optimal dosage, start with 1 inch, increase dose 1/2 inch at a time until headache occurs, then drop back to largest dose which doesn't cause headache. Apply to desired skin area with Dose Measuring Applicator. DO NOT USE FINGERS. Spread in thin, uniform layer. May be applied every 3-4 hours if necessary. Effective in control of angina pectoris, regardless of skin site of application, although patients may prefer chest site because anginal pain originates in this area. To stop treatment of anginal patients, gradually reduce dosage and frequency of application over period of 4-6 weeks to prevent characteristic nitroglycerin withdrawal reactions.
HOW SUPPLIED: 60-gram tubes.
CAUTION: Federal law prohibits dispensing without prescription.

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REFERENCES: 1. Davidov ME, Mroczek WJ: The effect of nitroglycerin ointment on the exercise capacity in patients with angina pectoris.

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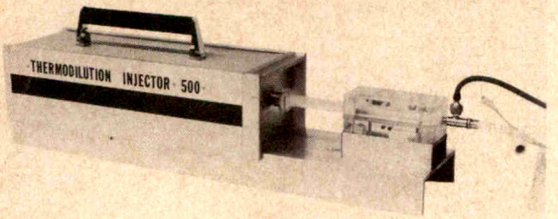

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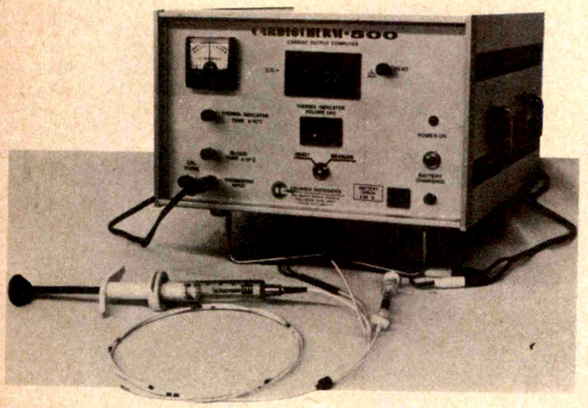

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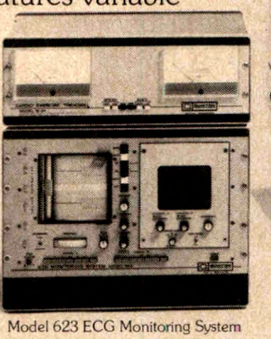

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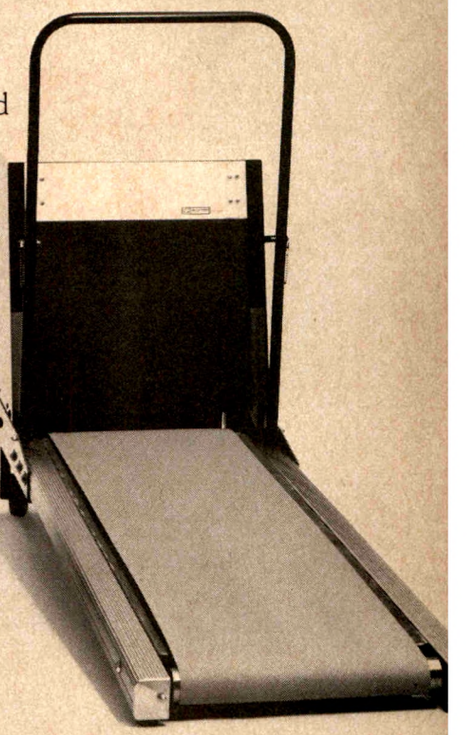

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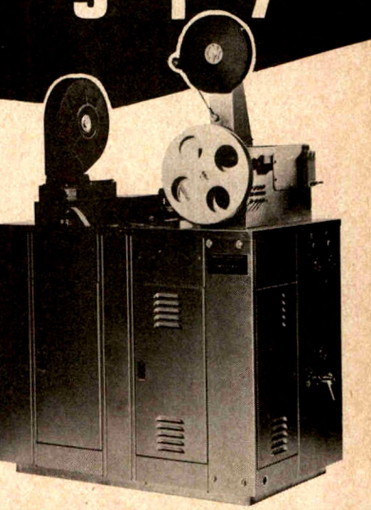

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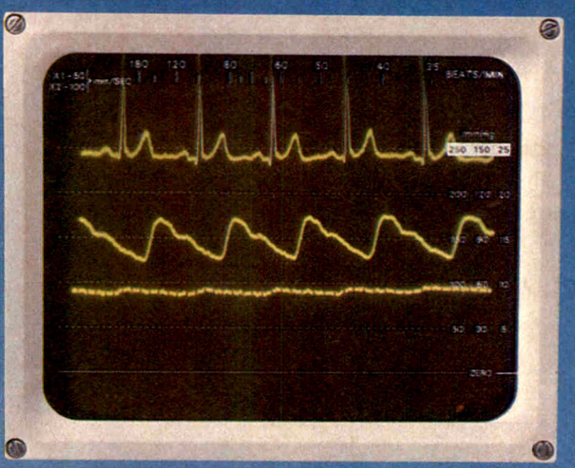

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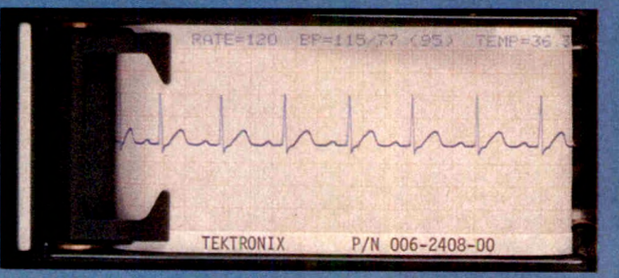

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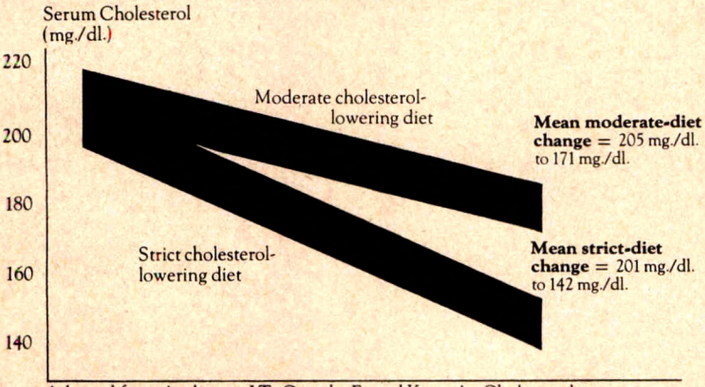

Adapted from Anderson, J.T., Grande, F., and Keys, A.: Cholesterol-lowering diets, J. Am. Diet. Assoc., 62:133, 1973.

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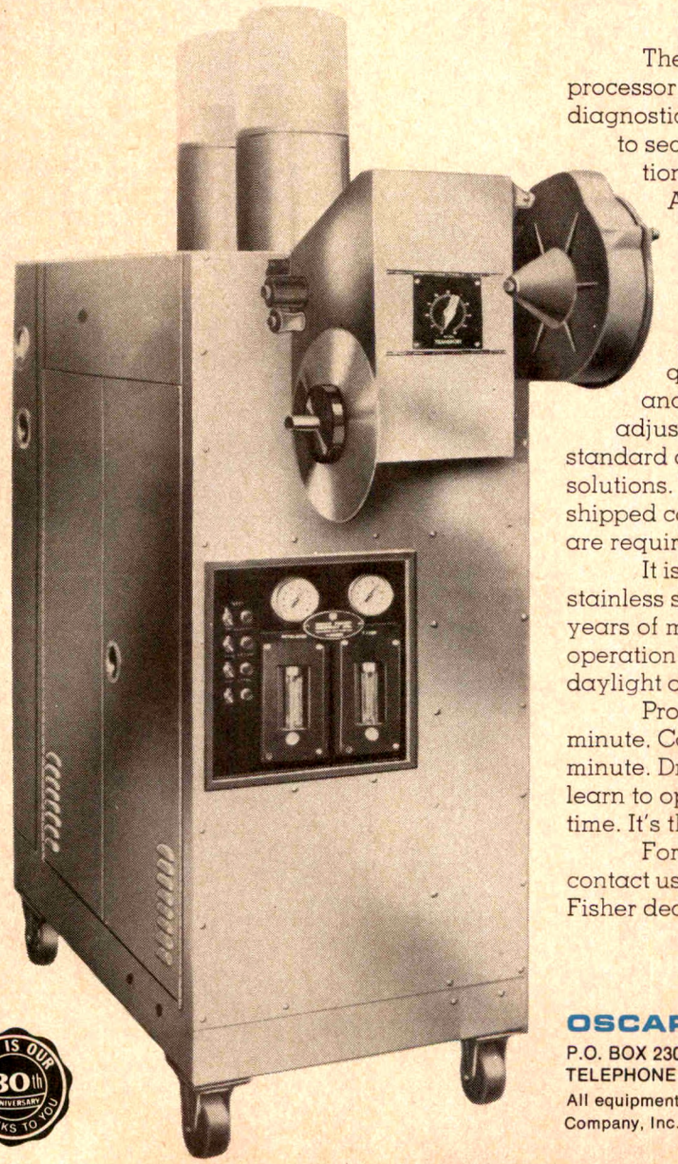

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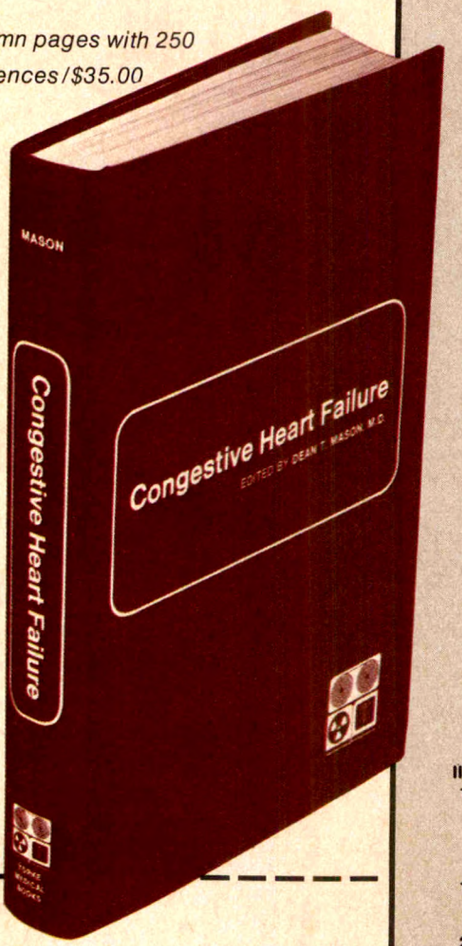

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School of Medicine
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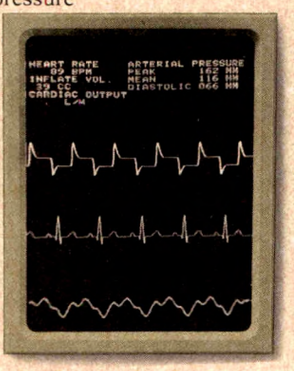

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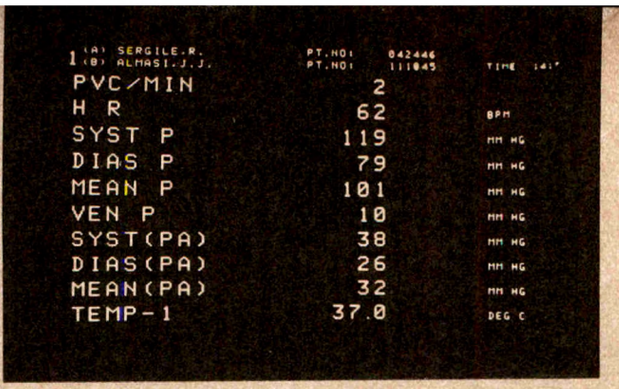
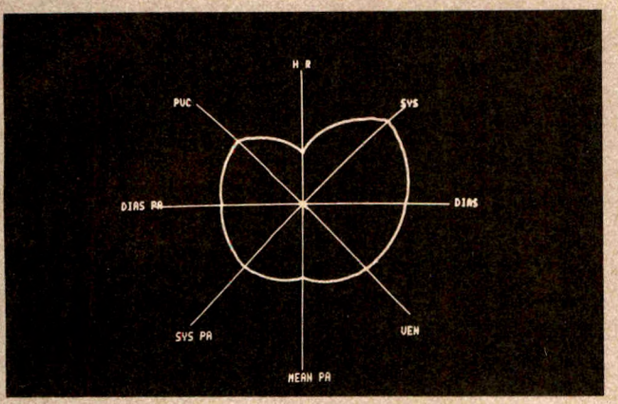
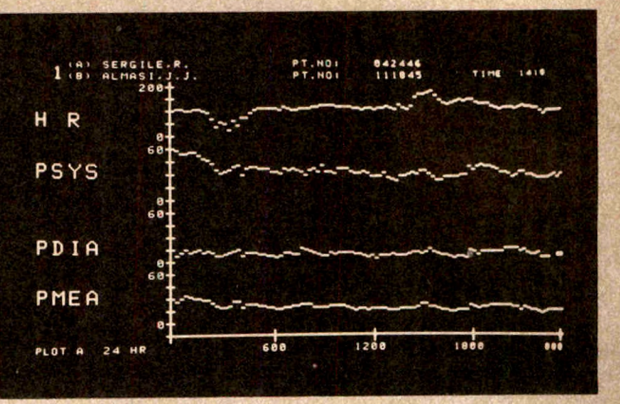


An abundance of patient data is one thing...





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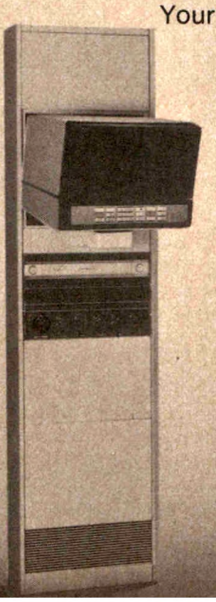

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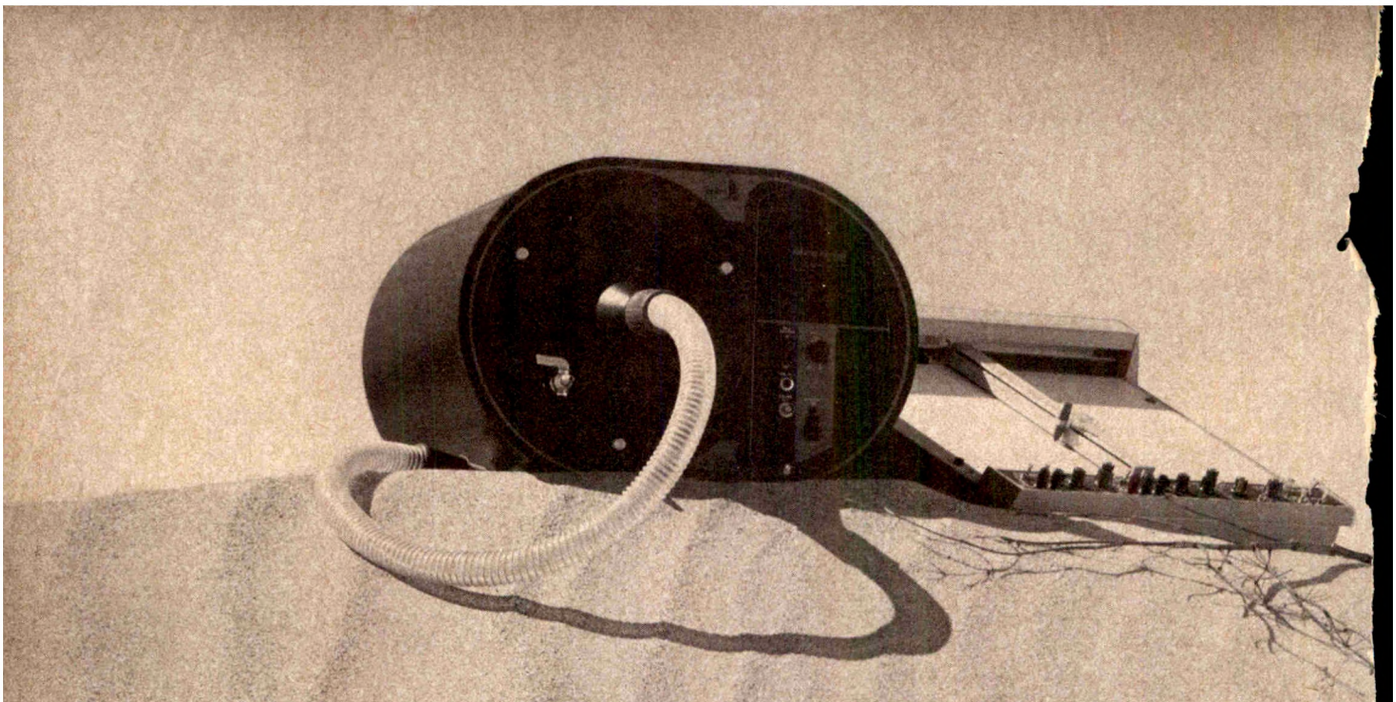

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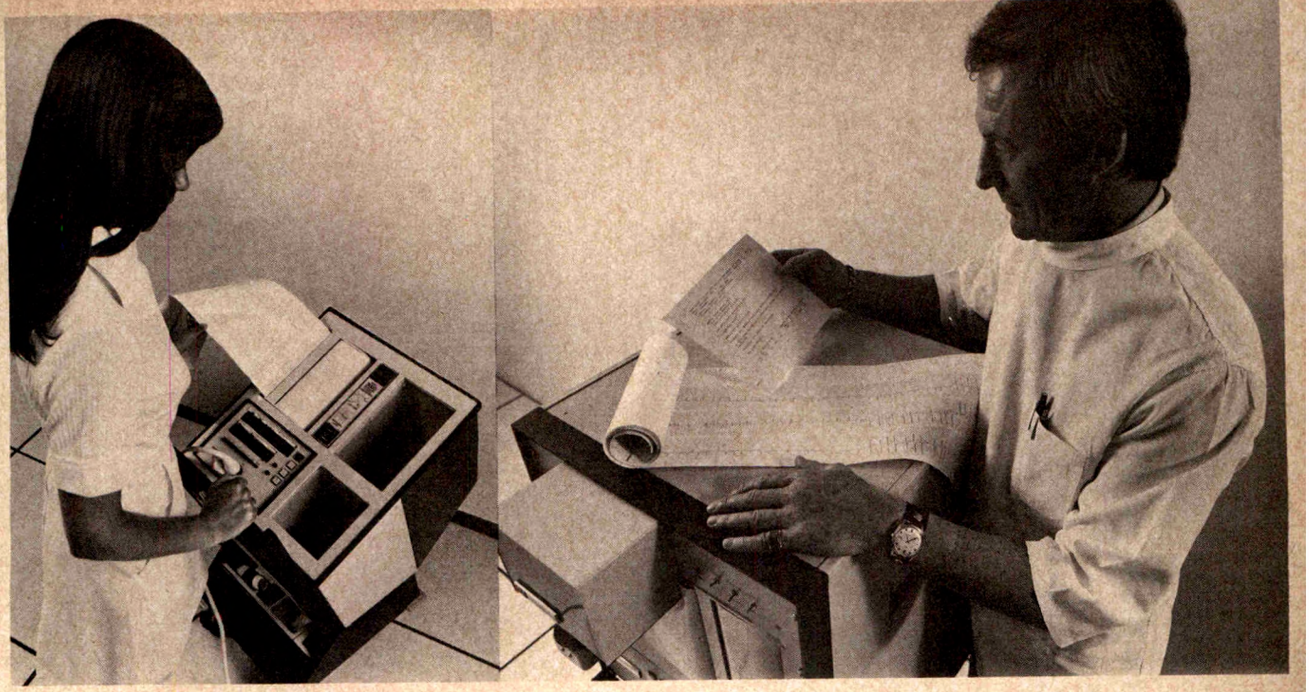

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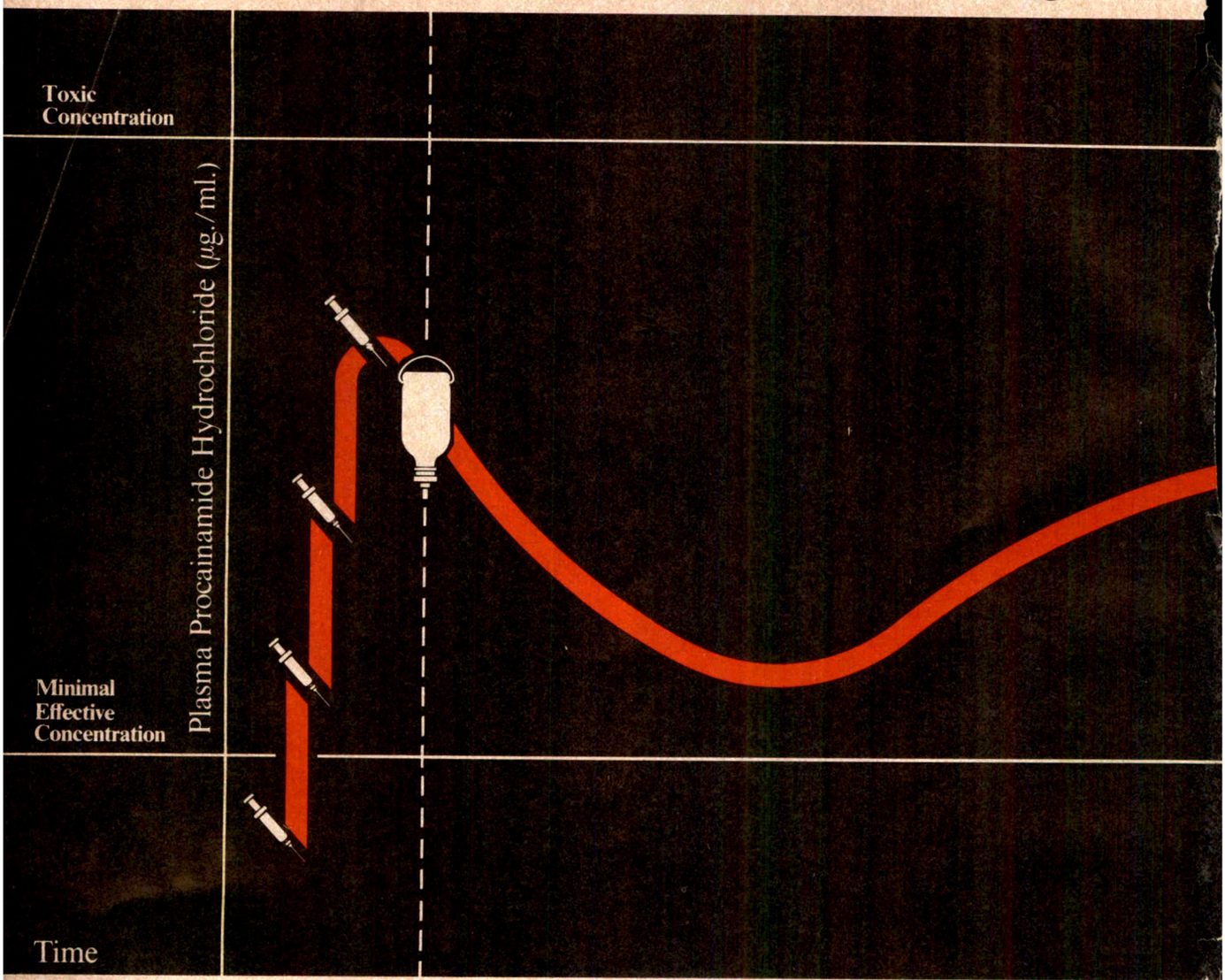

I.V. Injection:

100 mg. every 5 minutes
until arrhythmia suppressed
(up to a maximum dose of 1 gram)
to be administered at a rate
not exceeding 25 to 50 mg./minute.

I.V. Infusion:

2-6 mg. per minute

(Wyman, MG, Hammersmith L: Amer J Cardiol 33:661-667, 1974)

For ventricular arrhythmias, especially following M.I.

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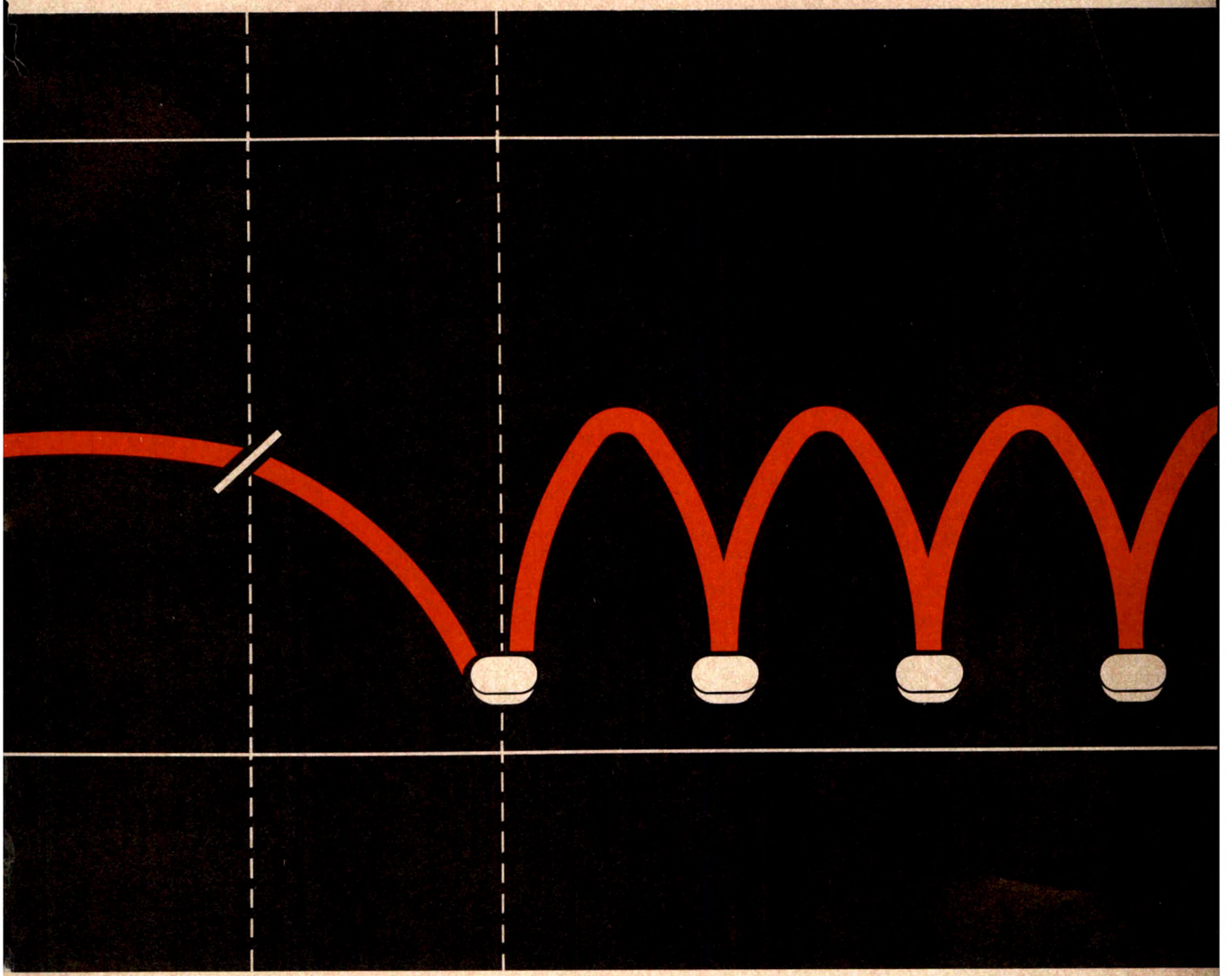
antiarrhythmic success.



Pause:
4 hours
before oral
regimen begun.

Oral tablets:
50 mg./kg./day

Pronestyl®
(Procainamide Hydrochloride)
through the entire therapeutic course

See next page for brief summaries.

A103

For Ventricular Arrhythmias

PRONESTYL® INJECTION
(Procainamide Hydrochloride Injection U.S.P.)

Description: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is a sterile aqueous solution providing 100 mg. or 500 mg. procainamide hydrochloride per ml. The 100 mg./ml. potency contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives. The 500 mg./ml. potency contains 0.1% methylparaben and not more than 0.2% sodium bisulfite as preservatives.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. *Intravenous use should be limited to extreme emergencies,* **the drug should be administered as a dilute infusion,** and the patient should be monitored electrocardiographically. The intravenous dose should not exceed 1 gram. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions.

How Supplied: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is available in 10 ml. vials providing 100 mg./ml. and in 2 ml. vials providing 500 mg./ml.

PRONESTYL® TABLETS
(Procainamide Hydrochloride Tablets)

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

Pronestyl Tablets (Procainamide Hydrochloride Tablets) are veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

Administration: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Adverse Reactions: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

How Supplied: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100. The 250 mg. and 500 mg. tablets are also available in bottles of 1000.

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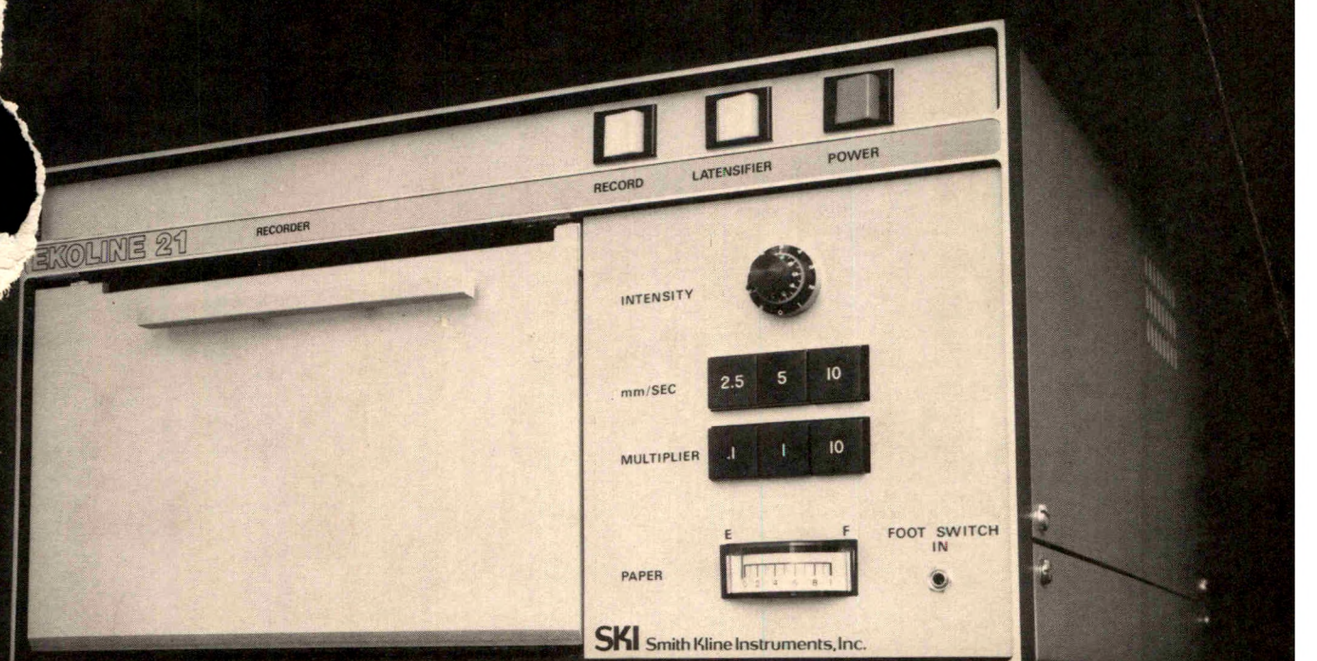
A new recorder to match the superior performance of the SKI Echo System.



The new Ekoline 21 Recorder brings advanced performance features to the SKI Echo System—the most outstanding system of its kind available today. The Ekoline 21 provides:

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For the broad spectrum of cardiac arrhythmias broad-range treatment... conversion and maintenance

CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance
- ☐ Full quinidine cardiodynamics
- ☐ Convenient B.I.D. or T.I.D. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases.

Well-tolerated, CARDIOQUIN Tablets are particularly suited for maintenance therapy, since the polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidin polygalacturonate) are indicated in the treatment of: premature atri and ventricular contractions; paroxysmal atrial tachycardia; paroxys mal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart block; maintenance therapy after electrical conversion of atrial fibri lation and/or flutter. CONTRAINDICATIONS: Aberrant impulses an abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ven tricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidin polygalacturonate 275 mg.) is equivalent in quinidine content to grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosag must be adjusted to individual needs, both for conversion and main tenance. An initial dose of 1 to 3 tablets may be used to terminat arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increase by ½ to 1 tablet (137.5 to 275 mg.) and administered three to fou times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one table morning and night will be adequate. SUPPLIED: Uncoated, score tablets in bottles of 50.

Purdue Frederick

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